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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 174

[EPA-HQ-OPP-2019-0508; FRL-10014-10]

RIN 2070-AK54

Pesticides; Exemptions of Certain Plant-Incorporated Protectants (PIPs) Derived from Newer Technologies

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: The Environmental Protection Agency (EPA) is proposing regulations that would allow for an exemption under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA) for certain PIPs that are created in plants using biotechnology, as long as their pesticidal substances are found in plants that are sexually compatible with the recipient plant and meet the proposed exemption criteria, ensuring their safety. The current exemption for PIPs is limited to PIPs moved through conventional breeding. EPA's proposed rule would allow certain PIPs created through biotechnology to also be exempt under existing regulations, in cases where those PIPs pose no greater risk than PIPs that meet EPA safety requirements, and could have otherwise been created through conventional breeding. The proposed rule also includes a process through which developers of PIPs based on sexually compatible plants created through biotechnology submit either a self-determination letter or request for EPA confirmation that their PIP meets the criteria for exemption. For increased flexibility in bringing PIPs to market, a developer can also submit both. EPA anticipates several benefits that may result from exempting these PIPs. These include lower costs

from reduced regulatory burden, increased research, development, and commercialization of pest control options for farmers, particularly in minor crops, and reduced use of conventional pesticides which could provide environmental benefits.

DATES: Comments must be received on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA-HQ-OPP-2019-0508, through the *Federal eRulemaking Portal* at *http://www.regulations.gov*. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute.

Due to the public health concerns related to COVID-19, the EPA Docket Center (EPA/DC) and Reading Room is closed to visitors with limited exceptions. The staff continues to provide remote customer service via email, phone, and webform. For the latest status information on EPA/DC services and docket access, visit *https://www.epa.gov/dockets*.

FOR FURTHER INFORMATION CONTACT: Anne Overstreet, Biopesticides and Pollution Prevention Division (7511P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; main telephone number: (703) 305-7090; email address: *BPPDFRNotices@epa.gov*.

SUPPLEMENTARY INFORMATION:

I. Executive Summary

A. Does this action apply to me?

You may be potentially affected by this action if you are a developer or registrant of a PIP. This proposal also may affect any person or company who might petition the Agency for a

tolerance or an exemption from the requirement of a tolerance for any residue of a PIP. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this action may apply to them:

• Pesticide and Other Agricultural Chemical Manufacturing (NAICS code 325320), e.g., pesticide manufacturers or formulators of pesticide products, importers or any person or company who seeks to register a pesticide or to obtain a tolerance for a pesticide.

• Crop Production (NAICS code 111), e.g., seed companies.

• Colleges, universities, and professional schools (NAICS code 611310), e.g., establishments of higher learning which are engaged in development and marketing of PIPs.

• Research and Development in the Physical, Engineering, and Life Sciences (except Nanobiotechnology) (NAICS code 541714), e.g., biotechnology research and development laboratories or services.

If you have any questions regarding the applicability of this action to a particular entity after reading the regulatory text, consult the technical person listed under **FOR FURTHER INFORMATION CONTACT**.

B. What action is the Agency taking?

EPA is proposing to exempt qualifying "PIPs based on sexually compatible plants created through biotechnology" from the requirements of FIFRA (except for the adverse effects reporting requirement at 40 CFR 174.71 and a proposed recordkeeping requirement at 40 CFR 174.73), and the residues of those PIPs from section 408 of FFDCA. PIPs are defined at 40 CFR 174.3 as "a pesticidal substance that is intended to be produced and used in a living plant, or in the produce thereof, and the genetic material necessary for the production of such a pesticidal

substance. [The PIP] also includes any inert ingredient contained in the plant or the produce thereof." EPA's proposal identifies a class of PIPs, i.e., "PIPs based on sexually compatible plants created through biotechnology," as those PIPs that are created through biotechnology and in which the pesticidal substance is found in plants that are sexually compatible with the recipient plant (i.e., the engineered plant) and that meet specific safety criteria. Although the amended definition proposed for "sexually compatible" specifically refers to a viable zygote formed through the union of two gametes, for this proposal EPA includes in its exemption also PIPs engineered in plants that are propagated vegetatively (e.g., potatoes and bananas). This approach aligns with the Agency's longstanding approach for exempting PIPs in vegetatively propagated plants created through conventional breeding and is consistent with the existing exemption of PIPs from sexually compatible plants created through conventional breeding. The proposed regulatory text for the exemptions from FIFRA and the FFDCA identifies a number of factors intended to ensure that the resulting PIP only produces a pesticidal substance found in plants that are sexually compatible with the recipient plant and thereby ensuring that these substances do not pose different risks to humans and the environment compared to those present in conventionally bred plants. While EPA believes the possibility of adverse effects from the PIPs proposed for exemption to be highly unlikely, it is important to note that the adverse effects reporting requirement under 40 CFR 174.71 would also apply to those PIPs proposed for exemption, as it does for currently exempt PIPs from sexually compatible plants. This requirement allows EPA to reconsider whether a PIP continues to meet the criteria for exemption upon learning of any adverse effects (e.g., injurious or deleterious levels in food plants). As described in the preamble of the July 19, 2001 *Federal Register* notice implementing 40 CFR 174.71 (66 FR 37772; July 19, 2001), the reports on human health or the environment alleged to

have been caused by the PIP would be made to EPA, but EPA will share such reports with the Food and Drug Administration (FDA), and as such, 40 CFR 174.71 is a means of ensuring that EPA and FDA can address any potential hazard. The proposed rule also includes a process through which developers are required to submit either a letter of self-determination or a request for EPA confirmation that a PIP based on a sexually compatible plant created through biotechnology meets the criteria for exemption.

C. What is the Agency's authority for taking this action?

This action is being proposed under the authority of FIFRA section 25 (7 U.S.C. 136w) and FFDCA section 408(e) (21 U.S.C. 346a(e)). FIFRA section 25(a)(1) authorizes EPA to issue regulations to carry out the provisions of FIFRA in accordance with certain procedures prescribed in that section. In addition, FIFRA section 25(b) allows EPA to promulgate regulations to exempt from the requirements of FIFRA any pesticide which the Administrator determines is "of a character which is unnecessary to be subject to [FIFRA] in order to carry out the purposes of [FIFRA]."

FFDCA section 408(e) authorizes EPA to initiate actions to establish tolerances or exemptions for pesticide chemical residues that meet the safety standard. See also the discussion in Unit IV.

D. Why is EPA taking this action?

Many plants, including those used for food, naturally produce substances that have pesticidal properties. Humans have relied on the presence of these substances for millennia to improve resistance in new agricultural and non-agricultural plant varieties by moving these traits between sexually compatible plants through conventional breeding. Because these substances may be at unsafe levels in undomesticated plants, rendering such plants inedible, breeders have

developed established procedures to ensure that the substances are kept to safe levels when introduced into plant varieties intended for human consumption. For the purposes of FIFRA, when these substances are introduced intentionally into a plant for a pesticidal purpose, the resulting product is considered a pesticide, and more specifically, a PIP.

In 2001, EPA published exemptions for PIPs moved through conventional breeding at 40 CFR 174.25, "plant-incorporated protectant from sexually compatible plant," and at 40 CFR 174.508, "pesticidal substance from sexually compatible plant; exemption from the requirement of a tolerance." For these exemptions, EPA defined sexually compatible plants as those for which "a viable zygote is formed only through the union of two gametes through conventional breeding." This includes those plants which can exchange genetic information unrestrictedly with each other through natural processes, such as pollination, and also those that are unable to exchange genetic information freely, but that are closely related enough that techniques employed in conventional breeding can facilitate their interbreeding. It specifically excludes plants developed through biotechnology. At that time, EPA did not exempt PIPs that are created through biotechnology and that are found in sexually compatible plants, but rather issued a supplemental proposal to exempt these PIPs because additional criteria needed to be developed. EPA ultimately withdrew that proposal in 2018 and indicated that, if the Agency were to pursue exemption of PIPs developed through biotechnology in the future, a new proposed rule would be issued (Ref. 1), as it became evident that exemption criteria should be developed given advances in biotechnology tools (see Unit II.C.2.).

Recent advances in biotechnology offer precise means by which genes coding for pesticidal substances can be inserted into a plant genome and allow for engineering of those genes that already exist within a plant. Due to these technical characteristics, PIPs can now be

created that are virtually indistinguishable from those created through conventional breeding. EPA was therefore able to develop specific exemption criteria that reflect the precise nature of new technologies. The proposed criteria are intended to identify a group of PIPs that would be exempt from both the requirements of FIFRA, with the exception of the adverse effects reporting requirement (codified at 40 CFR 174.71) and the recordkeeping requirement (proposed at 40 CFR 174.73), and that would also qualify for a tolerance exemption under the FFDCA. These PIPs are created through the use of biotechnology and, given the proposed regulatory criteria, pose no greater risk than the sexually compatible PIPs that are already exempt. EPA refers to this group as "PIPs based on sexually compatible plants created through biotechnology." The Agency's findings, including an assessment of the environmental and human health risks for this proposal, are presented in Unit VI.

EPA's proposal limits the type of plants, and thus the gene pool, that can act as a source of these exempt PIPs to those that are sexually compatible with the recipient plant. EPA is also proposing to amend the definition of "sexually compatible" to state that "a viable zygote *can* be formed through the union of two gametes through conventional breeding." EPA believes that this proposed definition is more biologically correct, because it refers to the ability of two gametes to form a viable zygote. This amendment would also allow for use of the phrase "sexually compatible" in the proposed exemptions. As a housekeeping task, EPA proposes to amend the existing PIPs from sexually compatible plants exemption at 40 CFR 174.25, along with its accompanying exemptions at 40 CFR 174.508 and 174.705, to clarify that those apply only to PIPs created through conventional breeding, thus differentiating them from those PIPs proposed for exemption that are created through biotechnology. These changes are necessary due to the amended definition of "sexually compatible" but will not change implementation of the existing

exemption for PIPs from conventional breeding. EPA's proposed exemptions are developed to be consistent with the current exemption at 40 CFR 174.25 for PIPs developed through conventional breeding techniques, and are expected to alleviate regulatory burden for developers that may wish to utilize biotechnology in creating pesticide products that are equivalent to those already exempt under FIFRA and the FFDCA.

On June 11, 2019, Executive Order 13874 (84 FR 27899, June 11, 2019) on "Modernizing the Regulatory Framework for Agricultural Biotechnology Products" was issued. The exemption proposed by EPA in this document is intended to further implement section 4(b) of that Executive Order, which directs the U. S. Department of Agriculture (USDA), EPA, and FDA ("to the extent consistent with law and the principles set forth in section 3" of the order) to "use existing statutory authority, as appropriate, to exempt low-risk products of agricultural biotechnology from undue regulation." Among other things, section 3 of Executive Order 13874 provides that regulatory decisions should be science-based and evidence-based, taking economic factors into account as appropriate and consistent with applicable law; that regulatory reviews should be conducted in a timely and efficient manner; and that biotechnology regulations should be transparent, predictable, and consistent. As part of the effort to implement Executive Order 13874, the USDA recently revised its regulations at 7 CFR part 340 through a rulemaking entitled "Movement of Certain Genetically Engineered Organisms." (85 FR 29790, May 18, 2020). In that rule, USDA amended its regulations regarding the movement (importation, interstate movement, and environmental release) of certain genetically engineered organisms in response to advances in genetic engineering and USDA's understanding of the plant pest risk posed by genetically engineered organisms, thereby reducing the regulatory burden for developers of organisms that are unlikely to pose plant pest risks. Both EPA and USDA use the

term “conventional breeding” in their respective rulemakings. However, it should be noted that each Agency uses the term in the context of its own regulations and that the term may have slightly different meanings depending on context.

The process for exemption under both the EPA proposal and USDA’s rule includes the option for developers to self-determine whether their product meets the criteria for exemption. EPA is proposing to require the developer notify EPA of that self-determination with a letter or, in the alternative, to request EPA confirmation that a particular PIP qualifies for exemption (developers may also submit both a self-determination letter and a confirmation request). Because developers of exempted PIPs will still be subject to FIFRA’s adverse effects reporting requirement and the recordkeeping requirement that is part of EPA’s proposed rule, EPA believes it is appropriate to require submission of a self-determination letter or a confirmation request in order to enable EPA to monitor compliance with EPA’s regulations and to take action to avoid adverse health impacts, if necessary.

E. What are the estimated incremental impacts of this action?

EPA has evaluated the potential incremental impacts of the proposed exemptions in the document entitled “Cost Analysis of the Proposed Rule Exempting Certain Plant-Incorporated Protectants (PIPs) from Registration” (Ref. 2), which is available in the docket, discussed in greater detail in Unit VI.A., and is briefly summarized here.

1. Benefits of the proposed exemptions.

The rule is estimated to reduce overall registration costs to developers of PIPs based on sexually compatible plants created through biotechnology, and the cost savings per product are approximately $444,000 – $459,000. Of the entities likely to develop PIPs based on sexually compatible plants created through biotechnology, EPA currently estimates that approximately

80% are small entities. These cost savings would be realized as EPA approval of new active ingredients are sought. The proposed exemption of PIPs based on sexually compatible plants created through biotechnology is likely to remove a potential barrier to market entry for small entities.

2. Costs of the proposed exemptions.

In the proposed rule, for a PIP to be exempt, a developer would be required to notify EPA through a self-determination letter or through a request for EPA confirmation that the PIP meets the exemption criteria. The proposed rule would also require that a developer maintain documents supporting its determination. Developer costs pertaining to the required exemption eligibility determination process and recordkeeping are estimated in the Agency cost analysis for the proposed rule. These costs are representative of developer labor and laboratory costs that would be required to generate the necessary information and data.

The developer cost of the exemption eligibility determination process is expected to be less than what would otherwise be required of a developer to obtain a registration. The cost analysis developed by the Agency is an overall cost reduction for developers of these types of PIPs. Adverse effects due to aggregate exposure to residues of pesticidal substances from PIPs based on sexually compatible plants created through biotechnology through the dietary, non-food oral, dermal and inhalation routes are highly unlikely, as the exemption eligibility determination process requires that the developer certify that the PIP meets the exemption criteria.

F. What should I consider as I prepare my comments for EPA?

1. Submitting CBI.

Do not submit this information to EPA through *regulations.gov* or email. Clearly mark the part or all of the information that you claim to be CBI. For CBI information in a disk or CD-

ROM that you mail to EPA, mark the outside of the disk or CD-ROM as CBI and then identify electronically within the disk or CD-ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that includes information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

2. Tips for preparing your comments.

When preparing and submitting your comments, see the commenting tips at *http://www.epa.gov/dockets/comments.html*.

II. Background

A. What are Plant-Incorporated Protectants (PIPs)?

Through natural evolutionary processes, plants develop mechanisms to resist pests. The mechanisms of resistance can be varied, including, for example, the production of metabolites that have toxic properties, biochemical cascades resulting in localized necrosis of plant tissue, or the production of substances in response to pest attack (Ref. 3). Humans have for approximately 10,000 years selected and bred certain plants for food, feed, and fiber, and a frequently selected characteristic has been the ability to resist pests (Ref. 4). When humans intend to use substances involved in these mechanisms in plants for "preventing, destroying, repelling, or mitigating any pest," the substances fall into the FIFRA definition of pesticide, regardless of whether the pesticidal capability evolved in the plant, or was introduced by conventional breeding or through the techniques of biotechnology.

A PIP is defined as "pesticidal substance that is intended to be produced and used in a living plant, or in the produce thereof, and the genetic material necessary for the production of

such a pesticidal substance. It also includes any inert ingredient contained in the plant or produce thereof" (40 CFR 174.3). For example, scientists can take the gene encoding for a pesticidal protein from a wild relative of corn and introduce the gene into another corn plant's genetic material. The plant then manufactures the pesticidal protein that kills the pest when the pest feeds on the plant. The genetic material necessary for the production of such a pesticidal substance also meets the FIFRA statutory definition of a pesticide, because such genetic material is introduced into the plant with the intent of ultimately producing a pesticidal effect. For transgenic PIPs, the relationship between the genetic material, the pesticidal substance, and the pesticidal effect has typically been linear (i.e., the genetic material inserted into the plant directly produces the pesticidal substance that confers the pesticidal effect). However, PIPs found in conventionally bred plants and their wild relatives can introduce additional biological complexity. For example, as described in the 2001 preamble (66 FR 37772; July 19, 2001), a PIP can encompass genetic material encoding an enzyme that ultimately leads to the production of the pesticidal substance (e.g., solanine). PIPs can also include traits intended for a pesticidal purpose that result from the loss-of-function of an existing plant gene where, for example, the inactivation of a gene coding for a plant receptor protein confers disease resistance. It is important to clarify that EPA regulates the modified genetic material that confers the loss-of-function trait as the pesticidal substance which is consistent with both the 1994 proposed rule preamble (59 FR 60496; November 23, 1994) and the 2001 final rule preamble (66 FR 37772; July 19, 2001) promulgating 40 CFR 174. EPA is requesting comment on whether a clarifying exemption specific to loss-of-function traits would be helpful (Unit VII.E.), although EPA considers these traits to be included under the current exemption at 40 CFR 174.25 and the proposed exemption at 40 CFR 174.26. For the sake of clarity, although the genetic material meets the statutory

definition of a pesticidal substance under FIFRA, in this preamble EPA uses "pesticidal substance" to mean a protein or other substance produced from genetic material that has pesticidal properties as per the definition at 40 CFR 174.3.

Although the PIP is regulated by EPA, the plant containing a PIP is not regulated by EPA. Additionally, many types of traits can be engineered into plants, but only those intended for a pesticidal purpose are PIPs. EPA does not regulate non-pesticidal traits under FIFRA or the FFDCA, or any other federal statutes. For example, EPA does not regulate traits introduced into a plant using biotechnology that enhance vitamin C content for nutritional purposes. Food from such a plant variety would be regulated by FDA.

B. How are PIPs regulated?

1. By EPA.

Because PIPs are pesticides, they are regulated under FIFRA and, to the extent necessary, FFDCA section 408. Under FIFRA, unless there is an applicable exemption, EPA is required to register PIPs so they may lawfully be sold and distributed. EPA evaluates each PIP application to determine whether its proposed use would cause unreasonable adverse effects on the environment. To avoid potential unreasonable adverse effects, the Agency may impose (and has imposed) terms and conditions on registration of PIPs (e.g., conditions to slow insect resistance). Additionally, EPA has the authority to take enforcement action with respect to any violations of activities subject to FIFRA. Under the FFDCA, EPA has established exemptions from the requirement of a tolerance for residues of PIPs in food. EPA evaluates each PIP to determine whether exposure to the residue of that PIP in or on food/feed is safe (i.e., there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide, which includes all anticipated dietary exposures and all other exposures for which there is reliable information).

2. By other federal agencies.

EPA is part of an interagency effort to improve, clarify, and streamline the regulation of biotechnology, including the regulation of plants developed using biotechnology that includes oversight by the USDA, FDA, and EPA. This approach was articulated by the White House Office of Science and Technology Policy in a policy statement in 1986 (51 FR 23302; June 26, 1986) and updated most recently in 2017 (Ref. 5). This document is known as the Coordinated Framework for the Regulation of Biotechnology. EPA is the federal agency primarily responsible for the regulation of pesticides. In fulfilling this mission, EPA works closely with the USDA, which has responsibilities under the Plant Protection Act, and the FDA, which has responsibilities under the FFDCA, including the enforcement of tolerances set by EPA under the FFDCA. EPA, USDA, and FDA consult and exchange information when such consultation is helpful in resolving safety questions. In addition to the Coordinated Framework, Executive Order 13874 requires EPA, FDA, and USDA to further coordinate their activities with regard to agricultural biotechnology. The PIPs that EPA is proposing to exempt are also exempted from regulation by USDA under 7 part 340 as revised by USDA's recently issued final rule titled "Movement of Certain Genetically Engineered Organisms." (85 FR 29790, 29791-92, May 18, 2020).

C. What actions did EPA take to prepare for this proposed rule?

1. Updated issue paper.

For this proposal, EPA updated an issue paper entitled "Natural Toxicants in Food from Plants" (Ref. 6). This issue paper summarizes and reviews the literature on the most common toxicants found in crop plants and discusses the regulatory status and current testing methods for each of those toxicants. Information from this issue paper was used in the Agency's safety

analysis for residues of PIPs based on sexually compatible plants created through biotechnology in or on food or feed. This document is available in the docket for this rulemaking.

2. Withdrawal of previous rule proposal.

In May 2018, the Agency withdrew a proposed rule entitled: "*Plant-Incorporated Protectants (PIPs); Exemption for Those Derived Through Genetic Engineering From Sexually Compatible Plants*" (Ref. 1). The proposed rule was withdrawn because the Agency determined that to exempt PIPs derived through genetic engineering from sexually compatible plants, more scientifically current criteria needed to be developed to reflect advances in genetics and molecular biology since the 2001 proposal. Consequently, EPA indicated that to pursue a future exemption, the Agency would issue a new proposed rule based on the types of products possible to create with newest technology rather than issue a final rule based on previous proposals (Ref. 1). As discussed in Unit VI., in developing this proposal for PIPs based on sexually compatible plants created through biotechnology, the Agency developed criteria that are scientifically more current and that more accurately describe the PIPs that would be exempted. Additionally, because the previous rule was withdrawn, the Agency will not consider comments made on the previous proposal. Therefore, if you believe a comment made regarding previous proposals is relevant to this proposal, you must resubmit the comment for this proposal.

3. Scientific advisory committees.

The FIFRA Scientific Advisory Panel (SAP) is a body of experts that provide independent scientific advice to EPA on issues related to pesticides, such as the impact to human health or the environment. FIFRA requires that EPA submit any proposed and final rule promulgated under FIFRA section 25(a) to the SAP for comment on the impact of the rule on human health and the environment. For this proposed rule, EPA requested that the FIFRA SAP

waive review of the proposal. In developing the scientific rationales in this proposal, EPA relied on previously provided advice from the FIFRA SAPs and analyses by the National Research Council of the National Academy of Science, Engineering and Medicine (Table 1).

Table 1.– Advice Sources for Key Concepts to Exempt PIPs Based on Sexually Compatible Plants Created Through Biotechnology.

Concept	Relevance to Current Proposal	Relevant Report
Exemption of PIPs based on sexually compatible plants created through biotechnology	Establishes the overall scope of the exemption. PIP would be developed by engineering a plant's genetic material to result in a PIP that could otherwise be found in the gene pool of the plant itself, e.g., in other varieties of the crop plant or in a sexually compatible relative. This scope should result in no novel dietary or environmental exposures.	FIFRA SAP 1992, 1993, 1994; NRC 2000. (Ref. 7, 8, 9, 10)
Criteria limiting the types of possible modifications introduced into a PIP in the plant	Establishes how much a gene could be modified (e.g., through truncations, deletions, or point mutations) while still retaining scientific support for the idea that humans have consumed the products of such genes for generations and that products of such modifications present no new dietary exposures.	FIFRA SAP 2004 *https://archive.epa.gov/scipoly/sap/meetings/web/html/101304_mtg.html* FIFRA SAP 2005 *https://archive.epa.gov/scipoly/sap/meetings/web/html/120605_mtg.html*
Introduction of a gene isolated from a plant in the same gene pool as the recipient plant	Establishes criteria to ensure that any introduced gene is part of the genetic diversity found in plants that are sexually compatible with the recipient plant.	FIFRA SAP 1992, 1993, 1994; NRC 2000. (Ref. 7, 8, 9, 10)
Ensuring expression profile falls within the gene pool of the plant and plants that are sexually compatible with the plant	Establishes criteria to ensure that any substance expressed from the modified genetic material is not expressed at higher levels, in different tissues, or at different developmental stages than seen in plants that are sexually compatible with the recipient plant.	FIFRA SAP 1993, 1994; NRC 2000. (Ref. 7, 9, 10)
Precision associated with newly developed techniques of genetic engineering, e.g., allowing genes present in the plant to be edited	Establishes criteria to ensure that only precise modifications are introduced into the modified plant – e.g., modifications of regulatory regions, allelic substitutions, introduction only of genes that falls within the genetic diversity found in plants that are sexually compatible with the recipient	NRC 2004; NASEM 2016, 2017. (Ref. 4, 11, 12)

	plant.	
Exemption eligibility determination process	Establishes streamlined procedures for developers to notify EPA of a PIP that qualifies for exemption.	NRC 2004; NASEM 2017. (Ref. 11, 12)

Two scientific advisory committees, the FIFRA SAP and the Biotechnology Science Advisory Committee (BSAC), a sister committee of equal stature later merged into the FIFRA SAP, offered advice that forms the foundation of EPA's current approach to PIPs. The Agency's 2001 final rule exempting PIPs from sexually compatible plants created through conventional breeding (40 CFR 174.25) and proposed exemptions (under both FIFRA and the FFDCA) for PIPs from sexually compatible plants derived through genetic engineering (see Unit II.C.2.) are based on advice from the FIFRA SAP.

The proposed exemptions in this document, are similarly based on advice provided by the FIFRA SAP, as the 1992, 1993, and 1994 FIFRA SAP reviews did not distinguish between PIPs moved among sexually compatible plants through conventional breeding and those moved through genetic engineering. Taking that advice into account, along with additional advice from NASEM reports in 2000, 2004, 2016, and 2017, this proposal describes the criteria that PIPs based on sexually compatible plants created through biotechnology, must meet to qualify for the proposed exemption. In response to the Agency's 1994 proposal to exempt PIPs from sexually compatible plants derived through genetic engineering, NASEM pointed out in its report in 2000 that the Agency's proposed language would exempt genetic material moved among plants in sexually compatible populations through the use of biotechnology without taking into consideration whether the moved genetic material would be expressed in the same pattern and at the same levels as occurs naturally in the plant (Ref. 10 at p. 129). This directly led to the Agency incorporating a criterion addressing expression levels and pattern in the proposed exemption requirements set out in this document. In addition to the advice from the 1992, 1993,

and 1994 FIFRA SAPs, EPA received additional advice from expert groups on scientific topics relevant to the current PIP proposed rule including, but not limited to, the 2004 and 2005 FIFRA SAPs that discussed how much a gene could be modified (e.g., through truncations, deletions, or point mutations) while still retaining scientific support for the conclusion that humans have consumed the products of such genes for generations and that products of such modifications present no new dietary exposures; and several reports from NASEM in 2004, 2016, and 2017 that describe the precision of modifications that can be achieved using new technologies for genetic engineering (Ref. 4, 11, 12).

The proposal in this document also describes an exemption eligibility determination process in which a developer must notify the Agency through either a self-determination letter or a request for EPA confirmation that the PIP meets the exemption criteria. For additional flexibility, EPA also proposes to allow a developer to submit both a self-determination letter and request for EPA confirmation, should they so choose. This proposed set of options takes into account advice from two reports by NASEM (Ref. 10, 12).

4. Stakeholder engagement.

EPA has participated in domestic and international events relevant to the proposed exemptions, all of which provided opportunities to engage with the regulated and research communities, the public, and other U.S. government agencies. Recent conferences and workshops include: Genome Editing - Putting Together the Pieces 2018; 2018 OECD Conference on Environmental Health and Safety of Applications of Gene Editing; Responsible CRISPR: Genome Engineering Conference 2019; North Carolina State University/ASTA Plant Breeding Workshop 2019; Plant Genomics & Gene Editing Congress: USA 2019; and the 2019 Global Regulatory Workshop on Plant and Animal Biotechnology Innovation. These meetings

supported EPA's horizon-scanning efforts for novel PIP products and presented engagement opportunities with the scientific and regulated community. These meetings also provided opportunities to develop practical knowledge of techniques and technology used in plant breeding and genetic engineering, which supported development of exemption criteria and rationale for assessing risks of PIPs created using biotechnology. Topics of discussion included plant breeding, technical aspects of biotechnology, and considerations regarding regulation and risk assessment of products.

III. Statutory Authorities and Regulatory Framework

EPA is authorized to regulate pesticides under two federal statutes. FIFRA regulates the sale, distribution, and use of pesticide products through a licensing (registration) scheme. FFDCA, among other things, regulates the safety of pesticide chemical residues in or on food and feed. EPA is proposing these exemptions under FIFRA section 25(b)(2) and FFDCA section 408.

A. What authority does EPA have under FIFRA section 25(b)(2)?

This section of FIFRA allows EPA to exempt, by regulation, any pesticide from some or all of the requirements of FIFRA, if the pesticide is of a character that is unnecessary to be subject to all the requirements of FIFRA in order to carry out the purposes of that Act (7 U.S.C. 136w(b)(2)). EPA interprets FIFRA section 25(b)(2) to authorize EPA to exempt a pesticide or category of pesticides that EPA determines (1) poses a low probability of risk to the environment and (2) is not likely to cause unreasonable adverse effects to the environment even in the absence of regulatory oversight under FIFRA.

In evaluating whether use of the pesticide poses a low probability of risk to the environment, EPA considers the extent of the potential risks caused by use of the pesticide to the

environment, including humans, animals, plants, water, air, and land. Potential risks to humans include dietary risks (which are assessed under the safety standard of the FFDCA section 408) and non-dietary risks, such as those resulting from occupational or residential exposure to the pesticide. EPA will not exempt pesticides under FIFRA section 25(b)(2) that fail to meet the required low probability of risk.

In evaluating whether the use of a pesticide is likely to cause unreasonable adverse effects on the environment even in the absence of regulatory oversight under FIFRA, EPA balances potential risks to human health and the environment from use of the pesticide against the potential benefits associated with its use. In balancing risks and benefits, EPA considers the economic, social, and environmental costs and benefits of the use of the pesticide.

B. What authority does EPA have under FFDCA section 408?

Under the FFDCA, food or feed containing pesticide residues may be considered adulterated (and subject to seizure if introduced, delivered for introduction, or received in interstate commerce) unless there is a tolerance or an exemption from the requirement of a tolerance in place covering those residues (21 U.S.C. 342(a)(1)(B)). EPA is authorized to establish tolerances (the maximum level) for residues in or on food or establish exemptions from the requirement of a tolerance, if it determines that the tolerance or exemption would be safe (21 U.S.C. 346a(b)(2), (c)(2)). Section 408 of the FFDCA defines "safe" to mean that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information" (21 U.S.C. 346a(c)(2)(A)(ii)). This includes exposure through drinking water, and residential and other indoor uses, but does not include occupational exposure. In addition, FFDCA section 408 requires EPA to give special consideration to exposure of infants

and children to the pesticide chemical residue in establishing an exemption and to "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue" (21 U.S.C. 346a(b)(2)(C)(ii)(I)) and (c)(2)(B)). FFDCA section 408(b)(2)(D) specifies other general factors EPA must consider in establishing an exemption (21 U.S.C. 346a(b)(2)(D)). In establishing a tolerance or an exemption from the requirement of a tolerance, the FFDCA does not authorize EPA to consider potential benefits associated with use of the pesticide chemical. Although EPA establishes tolerances or exemptions from the requirement of a tolerance under the FFDCA, FDA enforces these tolerances.

C. What is the relationship of FIFRA exemptions to the FFDCA section 408 standard?

EPA uses the FFDCA section 408 safety standard, as described in Unit III.B., in evaluating whether a pesticide used in or on food and feed meets the standard for exemption under FIFRA with respect to human dietary risk. A pesticide in or on food and feed presents a low probability of human dietary risk if it meets the FFDCA section 408 standard for an exemption from the requirement of a tolerance.

Additionally, a determination that a pesticide chemical meets the safety standard of FFDCA section 408(c) may also be relevant to whether a pesticide qualifies for a FIFRA section 25(b)(2) exemption with respect to human health risks arising from other routes of exposure. In determining whether a pesticide chemical residue is safe, EPA must consider "available information regarding the aggregate exposure levels of consumers . . . to the pesticide chemical residue and to other related substances, including dietary exposure under the tolerance and all other tolerances in effect for the pesticide chemical residue, and exposures from other non-occupational sources" (21 U.S.C. 346a(b)(2)(D)(vi)).

FIFRA, however, does not provide for exemption of a pesticide in or on food based solely upon consistency with the FFDCA section 408 exemption standard. At a minimum, EPA also must evaluate risks to the environment and risks arising from occupational exposure to humans and determine that such risks meet both exemption criteria (i.e., posing a low probability of risk to the environment and being not likely to cause unreasonable adverse effects to the environment even in the absence of regulatory oversight under FIFRA).

IV. Proposed Regulatory Framework for Exempting PIPs Based on Sexually Compatible Plants Created Through Biotechnology

In 2001, EPA created a regulatory structure at 40 CFR 174.21, for exempting PIPs from the requirements of FIFRA, other than the adverse effects reporting requirement at 40 CFR 174.71. First, the active ingredient of the PIP must meet codified criteria addressing FIFRA requirements listed in 40 CFR part 174, Subpart B; these provisions primarily deal with the pesticidal substance of the PIP and the genetic material necessary for production of that substance (40 CFR 174.21(a)). Second, when the PIP is intended to be produced and used in a food or feed crop, an exemption from the requirement of tolerance must be in place for residues of the PIP (40 CFR 174.21(b)). Third, any inert ingredient that is part of the PIP must be exempt under 40 CFR 174.705 (174.21(c)).

EPA is proposing to create an exemption from FIFRA requirements for certain PIPs based on sexually compatible plants created through biotechnology. These PIPs are created through biotechnology and their pesticidal substance is found in plants that are sexually compatible with the recipient plant. To satisfy the requirement of 40 CFR 174.21(a), EPA proposes to create a new section under subpart B for 40 CFR 174.26 containing criteria that an active ingredient of a PIP based on a sexually compatible plant created through biotechnology

must meet to qualify for the new exemption.

To meet the condition of 40 CFR 174.21(b), EPA is proposing to exempt from the requirement of a tolerance under the FFDCA residues of PIPs based on sexually compatible plants created through biotechnology that are present in or on food or feed. This exemption and the safety criteria that the residues must meet to qualify for the exemption will be codified in 40 CFR part 174, Subpart W with other PIP-related FFDCA exemptions.

Per 40 CFR 174.3, an inert ingredient is defined as "any substance, such as a selectable marker, other than the active ingredient, where the substance is used to confirm or ensure the presence of the active ingredient, and includes the genetic material necessary for the production of the substance, provided that genetic material is intentionally introduced into a living plant in addition to the active ingredient." Additionally, in 2001 EPA stated that "with regard to the enzymes, precursors, or intermediates in biosynthetic pathways necessary for anabolizing the pesticidal substance, EPA at this time considers them to be part of the plant-incorporated protectant because the substance is intended to "ensure the presence of the active ingredient"—i.e., it is an inert ingredient." EPA is therefore proposing to expand the scope of the existing inert ingredient exemption at 40 CFR 174.705 to include inert ingredients initiated through a modification made using biotechnology, as EPA believes the intermediary substances described in the 2001 quote would be included in this.

Other than these intermediary substances, the Agency does not expect other, more traditional inert ingredients (e.g., a gene coding for herbicide tolerance) in PIPs based on sexually compatible plants created through biotechnology. This is because older methods of biotechnology that have typically been used to create PIPs use a bacterial plasmid vector to incorporate a DNA construct into the genome of the plant. The DNA construct is an artificially

constructed segment of nucleic acid consisting of regulatory elements, the gene coding for the active ingredient, and sometimes a gene coding for an inert ingredient. Because the gene coding for the active ingredient and the gene coding for the inert ingredient are located on the same DNA construct and will therefore be incorporated into the plant genome together, the inert ingredient is able to confirm or ensure the presence of the active ingredient. However, newer biotechnology techniques, such as CRISPR, that are precise enough to create PIPs proposed for this exemption do not use DNA constructs in this way. Instead, these newer techniques allow developers to perform targeted edits to existing genes, and do not require the incorporation of inert ingredients in the same way as historically seen in transgenic PIPs. Modifications coding for substances similar to inert ingredients seen in transgenic PIPs (e.g., herbicide resistance) would instead be incorporated into the recipient plant genome independent of the active ingredient. Because newer techniques allow for these events to be introduced independently, the modification cannot confirm or ensure the presence of the active ingredient. The modification therefore would not meet the definition of an inert ingredient under 40 CFR 174.3 because it is an independent, non-pesticidal trait not regulated under FIFRA. EPA expects that any ingredients intentionally added during the development of PIPs based on sexually compatible plants created through biotechnology that are specific to the production of the active ingredient (e.g., guide RNA, DNA nuclease) would either be transiently transformed or would be removed (e.g., through segregation of the trait) during the breeding process. If these traits have not been removed from the final product the product would not meet the criteria proposed under the new 40 CFR 174.26 and would not qualify for the new exemptions. The Agency requests comment on whether there are any inert ingredients other than the intermediary substances described in the 2001 quote that will remain in the final plant products containing PIPs based on sexually

compatible plants created through biotechnology. If inert ingredients other than the intermediary substances described in the 2001 quote are identified in the responses to the previous request, the Agency also requests comment as to whether the inert ingredients in PIPs based on sexually compatible plants created through biotechnology require the proposal of an exemption that would be specific to those created through biotechnology and would allow developer flexibility in the nucleic acid sequence (see Unit VII.A.). EPA is also proposing to add a recordkeeping requirement and exemption eligibility determination process to 40 CFR 174.21 applicable to PIPs based on sexually compatible plants created through biotechnology that would require a developer to notify EPA that the PIP meets the criteria for exemption from the requirements of FIFRA under the conditions of 40 CFR 174.21 and to maintain supporting documentation of its determination. The exemption eligibility determination can be submitted in two, non-mutually exclusive ways: a self-determination letter or a request to EPA for confirmation of the self-determination.

V. Proposed Revisions to the General Provisions (Subpart A)

Provisions that apply to PIPs are codified in 40 CFR part 174, Subpart A. EPA is proposing several changes to these general provisions.

A. What are the proposed new definitions?

Definitions that apply to PIPs are codified in 40 CFR part 174, Subpart A, and EPA is proposing to add new definitions for "gene," "native allele," and "native gene." Only one term, "gene," is discussed in this unit. The other proposed definitions are discussed in detail in Unit VI.

EPA is proposing to define "gene" as meaning a "functional unit of heritable genetic material that is comprised of the genetic material necessary for the production of a substance."

All living organisms encode the substances they need to perform their normal metabolic functions in discrete units in their genome, called genes. This includes the pesticidal substances plants produce to defend against pests. Genes are further comprised of several functionally distinct regions within that unit that work in concert to produce the substance that is encoded by the gene's nucleic acid sequence. The two regions relevant to the criteria proposed to circumscribe PIPs based on sexually compatible plants created through biotechnology are the regulatory and coding regions. Together, they determine the function of a given gene within the plant. The sequence within the regulatory region of a gene determines the amount of substance that is produced and the spatiotemporal pattern of expression within the plant tissues. The coding region, which is the sequence that is ultimately transcribed, determines the identity of the substance that is produced from the gene (e.g., the amino acid sequence of a protein). Because the regulatory and coding regions of a given gene are inherited together as a single unit, they have evolved together over evolutionary time. In proposing the definition of a gene, the Agency clearly identifies and delineates the physical unit of the genetic material within the plant genome that encodes the substance and leads to the production of the pesticidal substance and, in doing so, restricts any genetic modifications made through biotechnology that would fall under the proposed exemption to the coding and regulatory regions. Defining the term "gene" was not necessary in the context of PIPs before this proposed exemption because previous methods employed to create PIPs, such as particle gun transformation, relied on the integration of a genetic construct, which included other genetic sequences in addition to a gene.

B. What is the proposed amendment to the existing definition for "sexually compatible?"

The term "sexually compatible" is currently defined at 40 CFR 174.3 as "when referring to plants, means a viable zygote is formed only through the union of two gametes through

conventional breeding." EPA is proposing to amend the existing definition for "sexually compatible" to instead state "when referring to plants, means a viable zygote can be formed through the union of two gametes through conventional breeding." EPA believes this amended definition is more in line with the biological definition of sexually compatible, in that being sexually compatible is widely accepted to mean that two organisms are *capable* of forming viable progeny. The amended definition also allows the Agency to use the term "sexually compatible" in the biological sense in the proposed exemption. The proposed clarification to the sexually compatible definition necessitates changes to the existing PIP from sexually compatible plant exemption at 40 CFR 174.25, along with its accompanying exemptions at 40 CFR 174.508 and 174.705; however, these changes do not result in modifications to the existing exemption for PIPs moved through conventional breeding. EPA discusses this proposed clarification in detail in Unit VI.F.

VI. Proposed Exemptions and Exemption Eligibility Determination Process (Subparts B, D, E, and W)

EPA is proposing to create an exemption from FIFRA requirements for certain PIPs based on sexually compatible plants created through biotechnology (described in Unit VI.A.) and to create a companion exemption from the FFDCA section 408 requirement of a tolerance for residues of certain PIPs based on sexually compatible plants created through biotechnology in or on food or feed (described in Unit VI.B.). EPA is also proposing to add a new subpart (subpart E) to 40 CFR part 174 that would codify the procedures and requirements for the new exemption eligibility determination process (described in Unit VI.C.). EPA is proposing a new section in subpart D, 40 CFR part 174.73, that would codify recordkeeping requirements for exemptions (described in Unit VI.D.). To accommodate the exemption eligibility determination process and

recordkeeping requirements, EPA is making some clarifying edits to 40 CFR 174.21 as described in Unit VI.E. Finally, EPA is also clarifying the relationship between the proposed exemptions for PIPs based on sexually compatible plants created through biotechnology and the exemptions currently at 40 CFR 174.25, 174.508, and 174.705 by modifying 174.25, 174.508, and 174.705 as described in Unit VI.F.

A. What is the proposed FIFRA exemption for the active ingredients of PIPs based on sexually compatible plants created through biotechnology?

1. What the proposed exemption covers.

EPA currently exempts PIPs from sexually compatible plants as described in 40 CFR 174.25. Because EPA had previously defined sexually compatible plants as including only those plants that create viable progeny through conventional breeding, the current exemption excludes PIPs created through biotechnology, even if they are equivalent to PIPs that could have been developed through conventional breeding. Technological advances surrounding genome editing (e.g., meganucleases, zinc-finger nucleases, transcription activator-like effector nucleases, and CRISPR-Cas nuclease system) allow for targeted, rapid, and precise changes directly to chromosomes of living cells (Ref. 12). These technologies allow for such precise editing of the genome, that the resulting genes can be indistinguishable from those found in a plant created through conventional breeding. Given the recent advances in technology, EPA was able to develop specific criteria proposed in a new section for 40 CFR 174.26 to exempt certain PIPs developed through the use of biotechnology that pose no greater risk than the currently exempt sexually compatible PIPs. The definition of sexually compatible is also proposed to be amended to refer to the ability of two gametes to form a viable zygote and thus be more biologically correct in stating that “a viable zygote *can* be formed through the union of two gametes through

conventional breeding." This amendment allows for use of the phrase "sexually compatible" in the proposed exemption.

The proposed criteria and supporting proposed definitions of "native gene" and "native allele" circumscribe the PIPs based on sexually compatible plants created through biotechnology that would qualify for the new exemption. The proposed criteria and the proposed definitions limit the types of PIPs that would be exempt to those that are found in plants that are sexually compatible with the recipient plant and meet specific safety criteria, thereby resulting in negligible risk of novel exposures. It is important to note that although the amended definition proposed for "sexually compatible" specifically refers to a viable zygote formed through the union of two gametes, for this proposal EPA includes in its exemption also PIPs engineered in plants that are propagated vegetatively (e.g., potatoes and bananas). This approach aligns with the Agency's longstanding approach for exempting PIPs in vegetatively propagated plants created through conventional breeding and is consistent with the existing exemption of PIPs from sexually compatible plants created through conventional breeding.

The definition of "native genes" limits the substances eligible for exemption to those found in plants that are sexually compatible with the recipient plant. As genes code for and produce substances, restricting the genes to only those found in plants that are sexually compatible with the recipient plant will limit the PIPs eligible for the new exemption to those found in plants that are sexually compatible with the recipient plant. The term "native" is used in the scientific literature in the context of cisgenes (e.g., a native promoter is a promoter endogenous to that gene). However, the Agency seeks comment on use of the term "native" in the names of "native gene" and "native allele" and associated definitions as the Agency does not mean to imply with the use of the term "native" that genes which originated through

conventional breeding techniques like mutagenesis would somehow be excluded from the proposed exemption. It is the Agency's intention that alleles found in sexually compatible plants that may have been created through conventional breeding would be included in the definition of "native allele" and "native gene."

Native genes comprising the gene pool of sexually compatible plant populations have been developed through the processes of mutation, selection, and genetic exchange. The proposed exemption captures ongoing diversification within gene pools by including within the proposed criteria a definition for native alleles. The definition of "native allele" is similarly limited to only those variants of native genes that are found in plants that are sexually compatible with the recipient plant.

EPA also proposes to capture additional ongoing diversification within existing native genes through the concept of differentially expressed genes. These are changes to a native gene that result in alterations in the amount of substance that is produced from that gene. An additional restriction on differentially expressed genes requires that the original pesticidal substance is preserved, which again limits eligible pesticidal substances to only those that are found in plants that are sexually compatible with the recipient plant. Native genes, native alleles, and differentially expressed genes represent the genetic diversity of sexually compatible plants; thus, these criteria limit exempt pesticidal substances of PIPs based on sexually compatible plants created through biotechnology to only those substances that are found in plants that are sexually compatible with the recipient plant.

For agricultural plants, those defined as being sexually compatible would include existing plant cultivars, landraces (i.e., a locally isolated variety of a domesticated plant species adapted to the natural and cultural environment in which it lives), and breeding lines, as well as plant

relatives that can breed with crops but are not currently used as agricultural plants. Including nonagricultural relatives in the sexually compatible pool is appropriate, as some traits found in nonagricultural wild relatives of cultivated plants, although not expressed in existing agricultural cultivars, have been accessible in plant breeding by conventional breeding techniques. For example, nonagricultural plant relatives may express defense mechanisms (i.e., pesticidal substances) that have been lost during domestication of crop plants and thus have not been entirely utilized in agricultural varieties.

Plant breeders have for many years been following established practices to ensure safety when moving genes into agricultural varieties from nonagricultural relatives, particularly from wild relatives, with no indication that substances resulting from these genes present higher levels of risk than those from genes moved only amongst agricultural varieties as long as those established practices are diligently followed (Ref. 13, 14, 15, 16). The ability to produce viable offspring is only possible in nature for organisms that possess many traits (and the genetic material encoding them) in common. Therefore, many of the traits present in agricultural plants and their wild relatives are likely to be similar in nature; the fact that the specific substance from the nonagricultural relative may not be found in the agricultural variety today does not mean that breeders do not have the experience and tools to ensure that it will be present in safe levels if transferred to the agricultural variety. Therefore, the likelihood is negligible that the transfer of such a substance via biotechnology from a nonagricultural relative to an agricultural one would pose a greater risk than if it were transferred through conventional breeding. The same logic defining the sexually compatible gene pool for agricultural crop plants also applies to other plants such as ornamental, turf, and semi-managed plants (e.g., trees).

EPA's proposed criteria and associated definitions are based on the ability of closely

related plants to hybridize and share genetic information. Because the substances produced by native genes and native alleles are present in sexually compatible plants, breeders have experience in ensuring that the substances will be at safe levels. This is also true for differentially expressed genes (i.e., genes with modified regulatory regions) because the proposed exemption criteria require that a) the substance produced from the genetic material be not different than what was being produced prior to the modification, b) the expression profile of the pesticidal protein does not exceed the limits seen in the sexually compatible plant population of the recipient plant. Although the proposed criteria allow for the use of biotechnology, the associated definitions are written to intentionally exclude "transgenes," which can be generally defined as derived from a source organism unable to share genetic material with the recipient plant through breeding. EPA does not consider transgenes to be native to the gene pool or a part of the genetic diversity of the recipient plant. Transgenic traits have been the focus of current PIP registration activities since 1995 (e.g., those derived from the bacterium *Bacillus thuringiensis*), and the registered PIPs generally present novel exposure scenario considerations for the transgenic trait.

2. Proposed criteria and associated definitions.

The Agency is proposing to define "native gene" to mean "a gene that is identified in the recipient plant or plants that are sexually compatible with the recipient plant; and has never been derived from a source that is not sexually compatible with the source plant." The phrase "has never been derived from a source that is not sexually compatible with the source plant" is meant to clarify that a PIP would qualify for the proposed exemption only if the native gene is present in the source plant as a result of conventional breeding. For example, if a bacterial endotoxin (e.g., from the source *Bacillus thuringiensis*) was engineered into plant "A" (the source plant), this bacterial endotoxin-based PIP would not qualify as a native gene to be used in plant "B" (the

recipient plant) under the proposed exemption, even if plant "B" is sexually compatible with plant "A". This is because while plant "B" and "A" can interbreed, the bacterium *Bacillus thuringiensis* (the source) and plant "A" (the source plant) are not sexually compatible. This proposed limitation on the source of the PIP therefore prevents a developer from claiming that a gene that encodes for a PIP is a "native gene" under the proposed definition when it is not, i.e., when the gene has been derived from a source that is not sexually compatible with the source plant. Given this explanation of the intent behind the phrase "never derived," EPA seeks comment on whether the use of the phrase in the proposed definition of "native gene" is clear.

"Native allele" means "a variant of a native gene that is identified in the genetic diversity of plants that are sexually compatible with the recipient plant." This definition is meant to clarify that the native allele must be a variant found in plants that are sexually compatible with the recipient plant, thereby limiting the potential pesticidal substances to those found in that population. By stating that the native allele is a variant of a native gene, the restriction that the genetic material cannot be derived from a source that is not sexually compatible with the source plant also applies to native alleles.

Equally important are two considerations, discussed in detail in the following sections, that are captured by the proposed criteria for 40 CFR 174.26 and that EPA believes together constitute the basis for meeting the FIFRA section 25(b)(2) standard for exemption: the pesticidal substance is found in plants that are sexually compatible with the recipient plant; and limitations on expression profile.

a. The pesticidal substance is found in plants that are sexually compatible with the recipient plant.

The proposed provisions for 40 CFR 174.26(a) delineate the scope of the new exemption

for PIPs based on sexually compatible plants created through biotechnology to only include those substances that are found in sexually compatible plants and substances with which plant breeders have experience. The regulatory text identifies two major categories that specify what will qualify as an exempt PIP pesticidal substance: (i) The insertion of new genetic material; and (ii) The modification of existing genetic material. Modifications of existing genetic material are further broken down into: modifications resulting in the differential expression of a gene, modifications resulting in a native allele, and modifications resulting in the differential expression of a native allele. The restrictions on the intended insertion or modification, as discussed in this section, ensure that no substance novel to plants that are sexually compatible with the recipient plant is produced.

By limiting the types of modifications permissible to those resulting in a pesticidal substance found in plants that are sexually compatible with the recipient plant (including substances already in the recipient plant), EPA can ensure that no substance novel to plants that are sexually compatible with the recipient plant is produced. This allows the Agency to ensure that PIPs based on sexually compatible plants created through biotechnology can meet the FIFRA section 25(b)(2) exemption standard because the modification would present a low risk of unreasonable adverse effects to humans and the environment due to the history of ensuring safe exposure through conventional breeding to the exempt substance. Criteria specific to the permissible modifications are described as follows.

i. The insertion of new genetic material.

For the insertion of new genetic material, 40 CFR 174.26(a)(1) proposes to limit insertions to native genes. EPA finds it important to include a native gene insertion option in its proposed exemption of PIPs based on sexually compatible plants created through biotechnology,

because there may be gene variability among sexually compatible plants. For example, plant genomes can be highly variable with the presence or absence of entire genes across different crop lines. If native gene insertion was excluded from the proposed exemption, EPA would be excluding a class of modifications that can be found in sexually compatible plant populations. For native gene insertion, the phrase proposed for 40 CFR 174.26(a)(1), "A native gene is engineered into a non-genic location of the recipient plant genome, resulting in a pesticidal substance identical to the pesticidal substance identified in the source plant," contains two criteria. First, the phrase "engineered into a non-genic location" is intended to preclude the insertion of the native gene into an existing gene. This is because the insertion of the native gene in the coding region of an existing gene within the recipient plant may then lead to production of a novel substance (e.g., a partial or modified substance) by the existing gene.

Second, the phrase "resulting in a pesticidal substance identical to the pesticidal substance identified in the source plant" ensures that the substance produced by the inserted native gene does not result in a substance with which breeders have no experience in preventing unsafe exposures. The requirement for an identical substance to be produced, rather than requiring the native gene to be composed of an identical nucleic acid sequence, allows for some flexibility in the nucleic acid sequence of the genetic material inserted into the recipient plant. It is important to allow for this flexibility because many nucleotide variations found within the coding region of the genetic material necessary for the production of a proteinaceous substance are silent, in that they do not result in changes to the amino acid sequence of the encoded protein. Thus, for proteinaceous substances, it is therefore permissible to insert a native gene that is composed of a nucleic acid sequence that is not identical to that found in the source plant so long as the pesticidal substance for which the nucleic acid sequence codes is identical to that

identified in the source plant. However, no such flexibility in the modification of the nucleic acid sequence of the coding region is granted for non-proteinaceous substances, i.e., in cases when the genetic material codes for the production of a type of RNA that is not subsequently translated into a protein (e.g., miRNA), as every nucleic acid in the coding region is reflected in the final sequence of the non-proteinaceous substance. For both proteinaceous and non-proteinaceous substances, flexibility is permissible in the nucleotide sequence of the regulatory regions. This allows for modifications to the expression level of the PIP resulting from the native gene insertion, so long as it meets expression profile criterion 174.26(b) as discussed in Unit VI.A.2.b.

ii. The modification of existing genetic material.

Proposed provisions for 40 CFR 174.26(a)(2) describe permissible modifications of existing genetic material and is further delineated into four possible categories: modifications resulting in the differential expression of a gene, modifications resulting in a native allele, modifications resulting in the differential expression of a native allele, and modifications resulting in the loss-of-function of an existing gene.

(A) Modifications resulting in the differential expression of a gene.

For the first category, the phrase proposed for 40 CFR 174.26(a)(2)(i), "the existing native gene in the recipient plant is modified to alter the amount of pesticidal substance produced without altering the identity of the pesticidal substance produced," limits the permissible modification in three ways. First, the modification must be made within the existing native gene in the recipient plant. The types of genes that can be modified only include those that have never been derived from sources that are not sexually compatible with the recipient plant; e.g., it is not permissible to adjust the expression level of a *Bt* gene. Second, the permissible modification is limited to changes that result in changes to the amount of pesticidal substance. While the

abundance of a substance in a plant is not solely determined by its level of expression (i.e., the amount of messenger RNA produced), it is reasonable to assume that they generally correlate, e.g., reducing the expression of a gene is expected to also reduce the abundance of the substance that is encoded by that gene (Ref. 17).

Third, the phrase "without altering the identity of the pesticidal substance produced" prevents modifications to the coding region of the gene that result in a partial or modified pesticidal substance. By requiring that the identity of the pesticidal substance be preserved, EPA can ensure that the identity of the substance produced by that gene remains the same as it was before the modification. In other words, a novel substance cannot be produced as a result of the modification; the only modification permitted is a change in the expression level of the substance produced by a gene. This position is consistent with the advice of the FIFRA SAP in the October 2004 meeting on "Issues Associated with Deployment of a Type of Plant-Incorporated Protectant (PIP), Specifically Those Based on Plant Viral Coat Proteins (PVCP-PIPs)," which stated that in the context of maintaining a "safe history" assumption, "only changes that affect an expressed protein are of concern and that changes to regulatory and untranslated regions are not relevant." (FIFRA SAP meeting held October 13-15, 2004, page 44 of minutes, Unit VI.A.3.a., Table 1). The statement that "changes to regulatory and untranslated regions are not relevant," indicates that modifications to those genetic regions do not result in a novel substance and therefore are not modifications of concern. Additional criteria surrounding permitted expression profiles are discussed in Unit VI.A.2.b.

(B) Modifications resulting in a native allele.

For the second category, the phrase in proposed 40 CFR 174.26(a)(2)(ii) "the genetic material that encodes the substance of the existing native gene is modified to result in a pesticidal

substance that is identical to the pesticidal substance encoded by a native allele of that gene," limits the types of modifications that could qualify for exemption. Like the restriction on differentially expressed genes, modifications to the recipient plant genome resulting in a native allele must be made within the existing native gene in the recipient plant. This criterion is intended to limit modifications solely to a single gene and would therefore exclude from exemption modifications that would affect more than one gene, e.g., those affecting chromosomal structure.

Although EPA recognizes that large-scale changes like translocations may be considered genetic variants, changes that affect the structure of chromosomes can affect many genes along the chromosome and are likely to disrupt or change the substances made by those genes. Insufficient information is available to allow the Agency to *a priori* conclude which structural changes would result in novel exposures, and therefore which changes may or may not result in unreasonable adverse effects. Thus, at this time, the Agency is unable to make a generic risk assessment on the consequences of chromosomal structural modifications and is not proposing an exemption that would allow for changes such as chromosomal inversions, translocations, or rearrangements. This does not preclude the Agency from registering these types of products or proposing an exemption at a later time should information become available that supports a determination of low risk.

The second half of the phrase, "to result in a pesticidal substance that is identical to the pesticidal substance encoded by a native allele of that gene," is another key limitation applied to native alleles and is based on the same concepts underlying the no novel exposure argument articulated for native genes in Unit VI.A.2.a.i. Briefly, requiring that the pesticidal substance produced in the recipient plant be identical to the substance encoded by the native allele ensures

that there will be no novel situations for plant breeders, and therefore no novel exposures. This requirement also allows for more flexibility in the modifications made to the recipient plant, in a way that restricting the nucleic acid sequence would not. Again, no such flexibility in the modification of the nucleic acid sequence of the coding region is granted for non-proteinaceous substances, i.e., in cases when the genetic material codes for the production of a type of RNA that is not subsequently translated into a protein (e.g., miRNA), as every nucleic acid in the coding region is reflected in the final sequence of the non-proteinaceous substance.

(C) Modifications resulting in the differential expression of a native allele.

For the third category, proposed 40 CFR 174.26(a)(2)(iii) states, "the existing genetic material is modified pursuant to both (i) and (ii)." This phrase is intended to indicate that it is also acceptable to create a differentially expressed native allele so long as the criteria under proposed 40 CFR 174.26(a)(2)(i) and 174.26(a)(2)(ii) are met.

(D) Modifications resulting in the loss of function of a gene.

For the fourth category, the phrase proposed for 40 CFR 174.26(a)(2)(vi), states "The existing native gene in the recipient plant is modified to lose function through the reduction or elimination of the substance encoded by that gene." EPA believes a separate exemption category to allow for instances in which the pesticidal trait in the plant is created via the loss-of-function of an existing gene helps clarify that the rule is intended to cover these types of modifications. To that end, EPA specifically uses the term "substance" rather than "pesticidal substance" for this exemption category when referring to the native gene product (e.g., protein). For example, a gene coding for a receptor protein may be modified to result in the loss-of-function of that protein to confer disease resistance. By specifying that the substance must maintain the same identity, EPA therefore prevents the production of modified proteins not previously identified in

the gene pool while still allowing for modifications in the coding region that ultimately prevent the production of a protein (e.g., premature termination codon). Additionally, modifications in the regulatory region of a gene would be allowed under the proposed exemption as these do not result in changes to the identity of the substance produced by the genetic material. EPA requests comment on whether an exemption category specific to loss-of-function traits (rather than including them in proposed 174.26) would be clearer (see Unit VII.E.).

b. Limitations on expression profile.

The proposed criterion at 40 CFR 174.26(b), "the pesticidal substance is not expressed at higher levels, in different tissues, or at different developmental stages than identified in a plant that is sexually compatible with the recipient plant," is a key limitation to prevent novel dietary and environmental exposures. The limitation on levels is important because endogenous plant compounds that result in plant resistance to pests can be toxic to mammals or other non-target organisms (Ref. 11). Limiting the expression profile of pesticidal substances to that found in a plant capable of being sexually compatible with the recipient plant ensures that the assumptions used to justify the proposed exemption (specifically, a long history of breeder experience with such substances and situations) support the statutory findings required to exempt PIPs based on sexually compatible plants created through biotechnology. For example, breeders will be able to ensure that modifications that lead to an increase in the expression of a substance are limited to levels accepted in conventional breeding because of their experience with the levels observed in plants that are sexually compatible with the recipient plant. The level of expression of pesticidal substances is expected to vary among sexually compatible plants depending on environmental conditions and due to intrinsic variations in their potential to express a substance (Ref. 17). Variation exists even among plants of the same variety due to different weather and soil

condition (Ref. 18). As such, limiting changes in the expression of a pesticidal substance not to exceed levels found within a sexually compatible plant supports meeting the FIFRA section 25(b)(2) exemption standard because such changes do not result in exposure levels not otherwise encountered through conventional breeding.

The proposed phrase also ensures that modifications allowed under the proposed exemption do not result in changes in the expression pattern of pesticidal substances. Specifically, this criterion ensures that pesticidal substances are only expressed in the same plant tissues and at the same developmental stages as what is found in a sexually compatible plant. For example, an insect toxin typically produced in the leaves of a plant would not meet the proposed exemption criterion if the plant is modified to produce the toxin in the nectar or pollen, as this may result in novel exposure of pollinators to the toxin. To ensure that the exempt PIPs are low risk and meet the FIFRA section 25(b)(2) exemption standard, EPA finds it necessary that pesticidal substances would not exceed expression levels or be expressed in different tissues or at different developmental stages from the exposure encountered among sexually compatible plants.

3. Risk analysis.

EPA considered several factors in determining whether PIPs based on sexually compatible plants created through biotechnology that meet the criteria under proposed 40 CFR 174.26 could be exempted from FIFRA requirements in order to meet the 40 CFR 174.21(a) requirement. That consideration relied upon the large body of knowledge that currently exists on sexually compatible plants and genetic diversity. The factors include: "(1) Low potential for novel exposures; (2) Low potential for levels of PIPs based on sexually compatible plants created through biotechnology to exceed levels found in sexually compatible plants; (3) Low potential

for PIPs based on sexually compatible plants created through biotechnology to move from cultivated plants to wild or weedy relatives through gene flow and increase weediness; (4) Low potential for occupational and non-occupational risks to humans; and (5) Low potential for resistance selection pressure posed by PIPs based on sexually compatible plants created through biotechnology to exceed that found in sexually compatible plants." EPA also evaluated considerations specific to newer biotechnology techniques related to PIPs based on sexually compatible plants created through biotechnology.

In addition to the analyses discussed in this unit for exemption under FIFRA, EPA also performed similar analyses for the proposed tolerance exemption under FFDCA discussed in Unit VI.B. EPA refers readers to the detailed discussions in that unit for information specific to the dietary safety of PIPs based on sexually compatible plants created through biotechnology.

a. Large body of knowledge.

In the issue paper entitled "FIFRA: Benefit and Environmental Risk Considerations for Inherent Plant-Pesticides" (Ref. 23), EPA describes a large part of the information base on nontarget plants, insects, birds, mammals and other herbivores that the Agency relied on for its evaluation of the potential effects of PIPs based on sexually compatible plants created through biotechnology on the environment. In addition, to understand the history of exposure of non-target organisms to substances found in nature that are equivalent to PIPs based on sexually compatible plants created through biotechnology, EPA used the large body of literature on the effect on humans of consumption of food from sexually compatible plants generated from epidemiological studies, nutritional assessments, animal model testing and biochemical studies (Ref. 24, 25, 26, 27, 28, 29, 30, 31, 32) to draw conclusions on the potential risk for animal non-targets, including birds and fish, which might consume food containing the PIPs proposed for

exemption. Testing in animal models can supply information that is extrapolated to make conclusions on the effect of a substance on humans; similarly, information and conclusions drawn in the dietary risk assessment on the effects on humans can be extrapolated to predict effects on non-human mammals and other animals in an assessment of environmental risk. In addition, there is a long history of humans using foods containing PIPs as food for domesticated and other animals, including birds and fish. EPA relied on this history of exposure and the large literature generated by a century of systematic studies of the constituents of food (Ref. 23) to assess PIPs based on sexually compatible plants created through biotechnology.

EPA also considered scientific knowledge from a number of disciplines, including plant genetics, plant physiology, phytopathology, biochemistry, ecology, evolutionary biology, genomics, and plant breeding. From the disciplines of plant physiology and biochemistry, EPA considered, for example, information on plant metabolism, the production of substances that may have a pesticidal effect, and conditions that may limit the production of such substances (Ref. 33). The Agency also used information from the science of phytopathology to characterize the pest resistance mechanisms in plants in order to understand the types of traits PIPs based on sexually compatible plants created through biotechnology may confer to recipient plants (Ref. 3). The sciences of ecology and evolutionary biology were considered for information on genetic diversity, mutation, and reproductive isolation mechanisms in populations (Ref. 34) to understand the types of genetic changes that are likely to occur when plants interbreed. Plant breeding and genetics were considered to describe the mechanisms of incompatibility and interbreeding (Ref. 35, 36), which aided EPA in determining when plants are likely to interbreed. Information from genomics and molecular biology were considered to understand the ability of newer biotechnology techniques to create traits equivalent to those found in conventionally bred

plants (Ref. 23, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46).

Finally, recommendations from several FIFRA SAPs and NASEM reports were considered in the development of the proposed exemption criteria for PIPs based on sexually compatible plants created through biotechnology, and when describing the types of genetic modifications in the recipient plant that are unlikely to result in novel exposure to humans and the environment (see Table 1 in Unit II.C.3.).

b. Low potential for novel exposure.

Given that PIPs based on sexually compatible plants created through biotechnology are intended to represent a subset of substances present in plants that plant breeders have experience with, EPA does not expect novel exposures from the substances involved.

Pesticidal traits, and the genetic material encoding them, have evolved and been developed in plant populations through the processes of mutation, selection, and genetic exchange among sexually compatible species (Ref. 47, 48). The ability to produce viable offspring is only possible for organisms that are genetically similar and possess many traits in common. Traits, and the genetic material encoding them, can be passed through a plant population by breeding. The mixing of genetic material that occurs through breeding results in sexually compatible plants having similar genetic material and similar traits. Due to the mixing of traits by mating, similar exposure scenarios are expected for plants that are capable of being sexually compatible, in other words, substances in sexually compatible plants are expected to be similar and therefore, only substances that plant breeders are already familiar with are expected to be present in sexually compatible plants. This conclusion is consistent with the 1992, 1993, and 1994 FIFRA SAP meetings that indicated that sexually compatible plants are more likely to have a common constitution than unrelated plants and thus movement of genetic material

between sexually compatible plants is less likely to lead to novel exposures (Ref. 7, 8, 23).

For agricultural plants, those defined as capable of being sexually compatible would also include existing plant cultivars, landraces, and breeding lines, as well as plant relatives that interbreed with crops but that are not currently used as agricultural plants. Plant breeders have for many years been moving genes into agricultural varieties from nonagricultural relatives with no indication that substances resulting from these genes present higher levels of risk than those from genes moved only amongst agricultural varieties (Ref. 13, 14, 15, 16). Therefore, the likelihood that the inclusion of nonagricultural varieties as potential source plants would pose an increased potential for novel environmental exposures from PIPs based on sexually compatible plants created through biotechnology is low.

If a population of sexually compatible plants normally possesses a pesticidal substance, organisms that encounter plants in that population have likely been exposed to the pesticidal substance in the past, perhaps over multiple generations. These past exposures, particularly if they occur over long periods of time, may lead to a degree of adaptation, or tolerance in the population of organisms exposed to the pesticidal substance (Ref. 49). Relatedly, the proposed exemption would not affect exposure patterns because the proposed criteria require that the pesticidal substance have an expression profile found in sexually compatible plants (e.g., the pesticidal substance is expressed in the same developmental stages or tissues). Any avoidance strategies of nontarget organisms (e.g., avoid eating certain parts of the plant) would still be protective in the case of PIPs based on sexually compatible plants created through biotechnology. Thus, the potential is low that PIPs based on sexually compatible plants created through biotechnology would pose novel exposures for organisms that typically encounter related plants.

Genetic diversity is created over time and EPA proposes to capture some of the ongoing diversification not identified in existing native genes or native alleles through the inclusion of changes resulting in the alteration of the amount of substance produced by existing genes, so long as no novel substance is produced and the substance is not produced in different tissues or at different developmental stages than those found in sexually compatible plants. Modifications that lead to differential expression levels of a substance are not expected to result in levels that exceed the boundaries of the variation found in sexually compatible plants due to physiological constraints that are related to energy expenditure (further discussed in Unit VI.A.3.c.). Therefore, the potential for novel exposures to occur with the differential expression of existing genes, or the movement of native genes and native alleles among sexually compatible plants, is low, because no substance novel to plants capable of being sexually compatible with the recipient plant will be produced, nor will the substance be found at higher levels, in tissues, or at developmental stages in which it is not currently found.

c. Low potential for levels of PIPs based on sexually compatible plants created through biotechnology to exceed levels found in sexually compatible plants.

EPA has evaluated whether there are likely to be quantitative changes in levels of PIPs based on sexually compatible plants created through biotechnology expressed by the recipient plant, such that adverse effects to the environment or to humans might occur (see Unit VI.B. for an analysis on human dietary risk). EPA has determined that the potential of such an event is low because the highest levels of pesticidal substances likely to be expressed with PIPs based on sexually compatible plants created through biotechnology are not likely to result in significantly different environmental exposure levels.

An analysis discussing the likely range of expression of PIPs in sexually compatible

plants was presented in an EPA issue paper, entitled: "FIFRA: Benefit and Environmental Risk Considerations for Inherent Plant-Pesticides" (Ref. 23). A summary of the analysis and how it applies to the proposed exemption is presented here. EPA first considered whether any increase in the levels of substances, including PIPs, that plants normally produce is likely to exceed the ranges normally found within and between plant varieties and uncultivated plants. The level of production of such substances normally varies among sexually compatible plants because of differences in potential to express a substance and environmental conditions. Indeed, variation is seen even among plants in the same variety because of differences such as weather and soil condition. For example, one report has shown an 8.3-fold variation in the amount of ascorbic acid in turnip greens depending on the degree of exposure to light (Ref. 18). EPA's proposal would exempt PIPs based on sexually compatible plants created through biotechnology that are not expressed above the range of variation on the basis that such exposures would not be considered novel. EPA considers that nontarget organisms, such as birds and insect pollinators, that associate with such sexually compatible plant populations have been and are currently being exposed to the upper levels of substances that might be used as PIPs based on sexually compatible plants created through biotechnology.

EPA considered the extent to which any substance can be increased in highly managed plants without unwanted effects on other, desirable characteristics of the plant such as yield or palatability of fruit. In general, breeders balance all of these characteristics in developing marketable plant varieties. Greatly increased levels of any substance, including PIPs based on sexually compatible plants created through biotechnology, generally would only be accomplished at the expense of the expression of other, agriculturally desirable traits due to physiological constraints related to energy expenditure in the plant (Ref. 23). A plant, like any

other living organism, has a finite energy budget, and can only harvest so much energy from the environment to allocate to all of its activities; therefore, a significant increase in the production of one substance, like a PIP, would reduce the energy that could be put towards the production of other substances critical to the plant's metabolism. Thus, there are practical considerations that limit the upper expression levels of a PIP based on a sexually compatible plant created through biotechnology to that found in a plant that is sexually compatible with the recipient plant. To codify this principle into regulatory text, EPA is proposing criteria in which the level of expression of the PIP based on a sexually compatible plant created through biotechnology is bound by the upper limit of expression of the pesticidal substance observed in a sexually compatible plant. By limiting the expression of PIPs based on sexually compatible plants created through biotechnology in this way, EPA can ensure that the exposures fall within the normal historical range of exposures with which plant breeders have experience limiting. EPA also considered whether the total expression (i.e., expression of the PIP across all plants capable of producing that PIP) would result in an adverse effect different than that possible through conventional breeding. Because the PIP based on a sexually compatible plant created through biotechnology could have otherwise been created through conventional breeding, EPA does not expect that the cumulative expression of a PIP based on a sexually compatible plant created through biotechnology would pose a higher risk than what is currently possible through conventional breeding.

The potential for exposure to PIPs is typically lower than for other types of pesticides because PIPs are produced within the living plant and used *in situ* in the plant. Other pesticides, such as conventional chemicals, must be applied to the plant, or near the plant. Because a PIP is produced and used within the plant, physiological constraints limit the amount of pesticidal

substance produced by the plant. Moreover, the routes by which other organisms may be exposed to the PIP are typically more limited, e.g., dietary exposure is likely to be the predominant route of exposure; there is a potential for dermal or inhalation exposure, although that likelihood is more limited (see Unit VI.A.3.e. for additional discussion of dermal and inhalation exposure in humans). In addition, PIPs are part of the metabolic cycles of plants, meaning they are biotic and subject to the processes of biodegradation and decay. Furthermore, PIPs are biodegradable to their constituent elements through catabolism by living organisms. Because they are readily degraded, PIPs do not bioconcentrate in the tissues of living organisms (Ref. 50) or persist in the environment. Given these characteristics, the potential for new exposures to occur, beyond direct physical exposures to the plant or plant parts, is limited for PIPs generally, including PIPs based on sexually compatible plants created through biotechnology.

EPA also considered whether variations of expression levels of PIPs based on sexually compatible plants created through biotechnology contained in semi-managed systems (e.g., trees) presented any novel issues for exposure to nontarget organisms (Ref. 23). Semi-managed systems received specific consideration because their semi-managed state can result in exposure to a larger variety of nontarget organisms compared to highly managed row crop systems. For the reasons stated in the preceding paragraphs in this unit, EPA anticipates that for such plants, levels of expression of PIPs based on sexually compatible plants created through biotechnology will continue to fall within the upper limit of expression currently observed for such substances in sexually compatible plants. Therefore, it is anticipated that the levels of PIPs based on sexually compatible plants created through biotechnology in semi-managed plants would not exceed the levels observed in sexually compatible free-living relatives (Ref. 23).

Finally, while not necessary to support the Agency's low probability of risk

determination under FIFRA, EPA did nonetheless consider the role of the plant breeding process in maintaining levels of substances in plants. Plants containing PIPs based on sexually compatible plants created through biotechnology will, as would plants in other development programs, pass through a post-development screening and selection process. During this process, plants with undesired or unexpected traits are identified and eliminated from further development. The development of new plant varieties, whether through conventional breeding or through biotechnology, begins with the production of a large number of plants containing the trait of interest. Plants are cultivated over several propagation cycles in order to identify those plants that inherit the intended phenotype across multiple generations while maintaining desirable agronomic characteristics such as uniform growth characteristics, fertility, and yield (Ref. 22). The screening and selection practices result in the selection of plants intended for commercialization that display desirable behavior, including desired levels of expression of various traits. Historically, these practices have proven to be reliable for ensuring safety and plants containing PIPs based on sexually compatible plants created through biotechnology are expected to also pass through these same screening and selection processes.

In conclusion, in its assessment, EPA considered the potential of variations in expression levels of PIPs based on sexually compatible plants created through biotechnology and whether those variations would present risk. EPA concluded that although variations in PIP expression levels will occur in response to environmental conditions in plants that interbreed, these variances are within exposure levels already encountered. The purpose of EPA's second criterion limiting expression levels to no higher than presently found in plants that are sexually compatible ensures that any exempt PIPs based on sexually compatible plants created through biotechnology would not pose a higher risk than what is currently found through conventionally bred plants.

Given the history of safe exposure to those substances, this criterion helps to ensure that exempt PIPs pose a low probability of risk from quantitatively different exposures.

d. Low potential for PIPs based on sexually compatible plants created through biotechnology to move from cultivated plants to wild or weedy relatives through gene flow and increase weediness.

Because PIPs based on sexually compatible plants created through biotechnology are produced and used in the living plant, EPA considered the possibility that the PIP may be transferred by hybridization from the crop plant to a cultivated, wild or weedy relative. A large volume of information is available in the public literature on this possibility and the likelihood of hybridization (Ref. 36, 51, 52, 53, 54, 55). EPA's issue paper entitled "Risk Considerations for Outcrossing and Hybridization" addresses these considerations for PIPs in plants in sexually compatible populations (Ref. 56). As the genes used to create the PIPs proposed for exemption produce the same substances as found in sexually compatible plant populations, EPA relied on this analysis to address this aspect of the assessment.

One of the considerations evaluated for this proposed exemption was whether a PIP based on a sexually compatible plant created through biotechnology could be transmitted to wild relatives through gene flow of genetic material. A second and more important consideration is whether such an outcrossing event could, in turn, increase weediness of the wild relative. For the following reasons, EPA concluded that the potential is low for weediness to increase in wild relatives through the flow of genetic material coding for a PIP based on a sexually compatible plant created through biotechnology.

There are several factors governing whether gene flow occurs, and thus governing the potential for hybridization between crops and their wild relatives (Ref. 53, 54, 57). First, genetic

barriers can prevent hybrids from forming, render them sterile, or reduce the fertility of hybrids, and thus restrict their contribution to subsequent generations. The strength of genetic barriers is correlated to the degree of evolutionary relatedness between the crop and wild relatives, with the barriers being stronger the more distantly related the plants. Second, geographic space is an effective barrier to hybridization. For instance, wild relatives with which corn can hybridize are restricted to Mexico and Central America. There is no potential of hybridization between domesticated corn and its wild relatives in other regions of the globe (Ref. 58). Third, temporal barriers such as time of flowering also affects hybridization, as hybridization cannot occur when there is no overlap in the time of flowering of cultivated and wild forms (Ref. 54, 57). For some species (e.g., peanut), the flowers do not ordinarily open, and self-pollination may be very near 100 percent; thus, hybridization between cultivated and wild forms is unlikely even if the cultivated and wild forms are synchronized in flowering and close enough geographically for pollen to move between them. Fourth, the ploidy level may differ between a crop and its relatives with many cultivated plants having higher ploidy than their wild relatives. Differences in ploidy levels can significantly reduce the likelihood that the cultivated plant and wild relative will form fertile hybrids (Ref. 54). Finally, some varieties of certain crop species, such as banana, are sterile, and thus are incapable of hybridizing not only with members of other species, but also with members of their own species (Ref. 59). For some crops in the United States, the probability of hybridization and gene transfer with the wild relative is zero, while for other crops, despite the variety of potential barriers to and selection against hybridization, gene transfer is possible.

However, even in instances where hybridization is possible, wild relatives generally tend to possess higher levels of resistance to pests and disease than do the cultivated members of those populations (Ref. 23). Wild relatives also tend to express a greater range of levels of

inherent plant defense compounds than do cultivated plants, including the production of higher levels of substances that could potentially be used as PIPs (Ref. 23).

If an agricultural or semi-managed plant containing a PIP based on a sexually compatible plant created through biotechnology hybridizes with a wild relative, it is unlikely that the levels of expression of the transferred PIP in the wild relative will be substantially increased. For reasons described in Unit VI.A.3.c., EPA anticipates that for agricultural, semi-managed, and feral plants, levels of substance expressed by the PIP based on a sexually compatible plant created through biotechnology will not exceed levels currently observed for the substance in sexually compatible plants (Ref. 23, 51). Thus, because the levels of expression of a PIP based on a sexually compatible plant created through biotechnology will not exceed levels currently observed in plant populations pursuant to proposed criteria, the potential for an increase in weediness in wild relatives is low should the wild relative acquire the exempted PIP trait.

e. Low potential for occupational and non-occupational risk to humans.

In general, PIPs are likely to present a limited exposure to humans. In most cases, the predominant, if not the only, exposure route will be dietary. Significant respiratory and dermal exposures are unlikely in non-occupational settings because most plant substances, including PIPs based on sexually compatible plants created through biotechnology, are expressed at relatively low levels and are found inside the cell, and therefore any human health risks in non-occupational settings are expected to be negligible. Although a potential for non-dietary exposure (e.g., dermal and inhalation) in occupational settings may exist due to the processing of plants resulting in increased exposure to intracellular substances like PIPs, EPA expects exposure to be low due to the relatively low levels of such substances in plants (Ref. 60). Given that PIPs based on sexually compatible plants created through biotechnology represent a subset

of substances present in sexually compatible plants that breeders have experience with and must be expressed at or below existing levels, in the same tissues, and at the same developmental stages, EPA does not expect novel exposures from the substances involved, as the sexually compatible plant sources have a history of being safe sources of genetic diversity for use in cultivated plants. Because these PIPs are indistinguishable from those found in a sexually compatible plant, which in many cases is a close relative or even the same plant species, existing allergen avoidance strategies for certain plants would still be protective.

Regarding dermal exposure, expressed substances of PIPs based on sexually compatible plants created through biotechnology may in some cases be present in sap or other exudates from the plant or the produce and thus may present some limited opportunity for dermal exposure to persons physically contacting the plant or raw agricultural food from the plant. Farmers and food handlers (e.g., individuals harvesting produce by hand, preparing food for sale, or stocking produce bins in grocery stores) or floral workers are those most likely to experience dermal contact with the substances on an occupational basis. However, because most plant substances, including PIPs, are expressed at relatively low levels and are found inside the cell, the level of exposure is still expected to be low.

Most of the substances that could be the subject of this proposed exemption are unlikely to pass through the skin to affect other organ systems or elicit allergenic sensitization (Ref. 60, reviewed in 61). The most common skin reaction to plant products is likely irritant contact dermatitis. These dermal reactions are generally mild, of a self-limiting nature or self-diagnosed, and self-treated (Ref. 60). Skin penetration of the substances comprising a PIP is dependent on several characteristics, including the substances molecular structure and hydrophobicity, accompanying mechanical irritation (e.g., thorns), the duration and site of contact, and the lipid

content of the skin. For most PIPs, human skin, which is composed of two layers, the epidermis and the dermis, is a natural barrier. The outer epidermal layer of the skin consists of dead cells in tight junctions (keratin) that provide a shield against elements in the outside world. The rapid shedding and replacement of the keratin layer serves as a further protective feature of the skin, as any damaged cells are quickly shed and replaced. For those PIPs based on sexually compatible plants created through biotechnology that might possess some properties that allow limited penetration of the skin, the potential amount passing through the outer epidermal layer of the skin (epidermis) is likely to be negligible (Ref. 60). Some irritant contact dermatitises are initiated by mechanical means which allow for limited penetration of the skin. For example, the small needle-like hairs of some plants (e.g., stinging nettle) penetrate the skin to deliver small doses of irritant toxins (e.g., histamine). However, plants with these characteristics are rare in cultivation, further limiting exposure (Ref. 60).

Importantly, PIPs based on sexually compatible plants created through biotechnology represent a subset of substances already present in related plants. PIPs based on sexually compatible plants created through biotechnology would therefore not be expected to alter predicted exposures of workers to plant proteins or other plant substances. Thus, dermal exposure to residues of PIPs based on sexually compatible plants created through biotechnology would not be predicted to alter exposure patterns in occupational settings.

Regarding inhalation exposure, PIPs based on sexually compatible plants created through biotechnology may in some cases be present in pollen, and some individuals (e.g., those working on farms in nurseries or other plant-growing areas) may be exposed through inhalation to wind-blown pollen. When present in pollen, the pesticidal substance is likely to be integrated into the tissue of the pollen grain. The likeliest impact of pollen exposure is rhinitis, or inflammation of

the mucous membranes lining the nose, resulting in symptoms like nasal congestion, sneezing, itching, post-nasal drainage, and runny nose. This proposed exemption will not change current exposures or affect strategies for dealing with reactions to PIPs based on sexually compatible plants created through biotechnology that may be aero-allergens or irritants (Ref. 60).

Pollen grains are solid, insoluble particles of sufficiently large diameter that they are filtered out in the nasopharynx or in the upper respiratory tract (Ref. 60), from which they are generally swallowed into the gastrointestinal tract. The gastrointestinal surface forms a barrier between the body and the lumenal environment and is often described as having two components: "(1) The intrinsic barrier is composed of the epithelial cells lining the alimentary canal and the tight junctions that tie them together, and (2) The extrinsic barrier consists of secretions and other influences that are not physically part of the epithelium, but which affect the epithelial cells and maintain their barrier function." Regarding the intrinsic barriers, the alimentary canal is lined by sheets of epithelial cells that form the defining structure of the mucosa and establish the basic gastrointestinal barrier. Regarding the extrinsic barriers, the gastrointestinal epithelium is coated with mucus, which is synthesized by cells that form part of the epithelium. Mucus contributes to barrier function in several ways by slowing the diffusion of molecules. Additionally, molecules in food, including edible plant tissue, are too large to be absorbed by the gastrointestinal tract and are broken down into smaller molecules to be absorbed and utilized by the body. Plant materials such as pollen are also subjected to the processes in the digestive tract that reduce larger molecules to smaller constituents that can be absorbed by the membranes of the small intestine.

Importantly, pollen characteristics (e.g., wind vs. insect dispersal, amount produced) are often maintained within plant families, as is necessary for successful breeding to occur.

Therefore, PIPs based on sexually compatible plants created through biotechnology should not alter already established characteristics of any particular species. In cases of occupational rhinitis, these PIPs would not be expected to significantly alter already established patterns of exposure to occupational dusts.

f. Low potential for resistance selection pressure posed by PIPs based on sexually compatible plants created through biotechnology to exceed that found in sexually compatible plants.

A component of EPA's oversight historically for PIPs created through biotechnology has been the requirement for registrants to implement an insect resistance management plan. Transgenic *Bacillus thuringiensis (Bt)* PIPs are likely at greater risk for insects developing resistance than many conventional pesticides targeting the same insects because *Bt* PIPs are expressed throughout all plant tissues for the entire lifespan of the plant compared to conventional pesticides, which typically have shorter periods of efficacy and are applied when pests are likely to cause yield loss. To address resistance management due to increased exposure, the Agency has required detailed information for *Bt* PIPs (e.g., dose expression levels, cross-resistance potential, modeling scenarios) alongside terms of registration (e.g., resistance monitoring programs, remedial action plans, compliance assurance, and grower education activities).

As mentioned in the previous paragraph, the risk of resistance to *Bt* PIPs primarily stems from increased exposure to the PIP from expression across plant tissues and across the plant lifespan, which are achieved due to transgenic regulatory elements used in the creation of the PIP. However, in the case of PIPs based on sexually compatible plants created through biotechnology, the potential to develop resistance is lower than that of *Bt* PIPs due to the

limitation on expression profile (e.g., same tissues and developmental stages) to be within what is found in sexually compatible plants. EPA does not anticipate an increased resistance risk posed by PIPs based on sexually compatible plants created through biotechnology compared to those developed by conventional breeding. The proposed rule does not require specific resistance management plans from developers of PIPs based on sexually compatible plants created through biotechnology that qualify for the new exemption.

g. Are there any considerations associated with newer biotechnology techniques?

Newer biotechnology techniques using present-day genome editing techniques (e.g., CRISPR, zinc-finger nucleases, transcription activator-like effector nucleases, oligonucleotide-directed mutagenesis) can present some additional considerations beyond those discussed previously, and these were taken into consideration in developing the proposal to exempt PIPs based on sexually compatible plants created through biotechnology from FIFRA requirements in order to meet the requirement at 40 CFR 174.21(a). Present-day genome editing techniques allow for precise modifications to the plant genome such that the PIP in question meets the proposed criteria. These new technologies can aid in plant breeding and result in varieties indistinguishable from those developed through conventional breeding (Ref. 12).

Although genome editing technologies allow for more precise editing or insertion compared to older technologies, there is still a possibility of unintended modifications, also called "off-target" mutations. With genome editing technologies, off-target mutations may occur when the genome editing machinery cuts DNA at sites that share sequence similarity with the actual target sequence. However, off-target mutations may occur as a result of any form of plant breeding, including conventional breeding, and an off-target mutation is not necessarily significant in a specific PIP/plant combination with regard to food, feed and/or environmental

risk. In plants, off-target mutations can largely be removed by backcrossing, if necessary, regardless of the method by which they were introduced (Ref. 62). It is very likely that the off-target mutation and the desired trait are inherited separately, which allows for developers to select plants that have the desired trait, but that do not have the off-target mutation.

A recent comparison of single-base pair substitution mutations resulting from plant breeding technologies found that the number of mutations detected after genome editing was not significantly different from what was found after routine tissue culture (Ref. 63). This analysis supports the conclusion that off-target mutations from genome editing are not inherently different or riskier than off-target mutations occurring through other forms of plant breeding. In addition, recent studies in rice and maize found that compared to the inherent variation found in the plant, mutations resulting from genome edited off-target mutations were negligible and far fewer (Ref. 64, 65).

The majority of unintended changes at the genomic level, whether due to off-target mutations from plant breeding technologies or through natural mutations, do not result in significantly deleterious effects to the plant at the phenotypic level (Ref. 4). This is primarily due to the highly plastic nature of plant genomes (Ref. 66, 67, 68). The small percentage of unintended changes that do result in significant deleterious effects are far more likely to produce an effect deleterious to the plant itself (e.g., stunted growth) than a novel exposure to humans or the environment (Ref. 34). Although EPA only regulates the PIP, FDA regulates the remainder of the plant for food safety (see Unit II.B.). In the context of the genetic material encoding the PIP, off-target mutations in the coding region resulting in protein-level changes would not be eligible for exemption based on the proposed criteria requiring that the substance be the same as identified in a source plant. Off-target mutations in the regulatory region would not be

considered a significant risk due to the same rationale allowing for modifications to regulatory regions as described in Unit VI.A.2.a. EPA therefore considers off-target mutations resulting from genome editing technologies to present a negligible risk to the environment in the context of PIPs based on sexually compatible plants created through biotechnology.

h. FIFRA section 25(b)(2): Preliminary statutory finding.

EPA preliminarily concludes that PIPs based on sexually compatible plants created through biotechnology as described for proposed 40 CFR 174.26, warrant exemption under FIFRA section 25(b) because these substances are of a character that is unnecessary to be subject to all the requirements of FIFRA to carry out the purposes of the Act. Specifically, EPA has preliminarily concluded that PIPs based on sexually compatible plants created through biotechnology that meet the exemption criteria pose a low probability of risks to humans and the environment.

As discussed in Unit VI.A.3., EPA has preliminarily concluded that PIPs based on sexually compatible plants created through biotechnology that meet the exemption criteria pose a low probability of non-dietary risk to humans and the environment. As explained in this preamble in Unit VI.B., EPA has also determined that there is a reasonable certainty that no harm will result from aggregate exposure to the residues of such products, including all anticipated dietary residues and all other exposures for which there is reliable information. As such, EPA has preliminarily determined that use of PIPs based on sexually compatible plants created through biotechnology is not likely to cause unreasonable adverse effects on the environment and humans in the absence of regulatory oversight other than the adverse effects reporting requirement in existing 40 CFR 174.71. Based on the low probability of the potential risks coupled with the proposed exemption eligibility determination process, EPA anticipates

minimal societal benefits would be gained by imposing the full degree of oversight associated with FIFRA registration (see Unit VI.A.4. for additional information on benefits). Finally, the adverse effects reporting requirement at existing 40 CFR 174.71 provides a mechanism that could alert the Agency to information regarding adverse effects associated with a PIP based on a sexually compatible plant created through biotechnology. Based on the information available, the benefits of exempting PIPs based on sexually compatible plants created through biotechnology from FIFRA outweigh the potential risk associated with these PIPs (risk that is low).

4. Benefits.

This unit summarizes the benefits that are described in greater detail in the cost analysis (Ref. 2). This cost analysis quantifies registration or Pesticide Registration Improvement Extension Act of 2018 (PRIA) related fees as required by FIFRA. These fees represent savings to developers if the proposed exemption becomes final.

The direct benefit of the proposed rule is the reduced regulatory burden associated with developing and marketing a PIP based on a sexually compatible plant created through biotechnology. The proposed exemption may encourage more research and development in this area of biotechnology and better enable firms of all sizes to engage in the development of these types of PIPs.

Entities that support major crops or larger markets can more easily absorb fixed registration costs. As a portion of the total costs of researching and developing a new active ingredient, registration costs often represent a small proportion of the overall costs of bringing a product to market. However, an outlay of fixed registration costs can be significant for a firm that supports minor crops. Removal of registration costs for these entities can be significant, so smaller entities may feel the most regulatory relief as a result of this rule.

Crop varieties modified for greater pest and disease resistance could also reduce the use of externally applied pesticides, which in turn could reduce farm expenditures and provide environmental benefits. Finally, the proposed exemption would also reduce the burden on the Agency to review applications for registration.

Exempting PIPs based on sexually compatible plants created through biotechnology from registration while also promulgating an exemption from the requirement of an FFDCA tolerance for residues of such PIPs in or on food or feed has an estimated incremental cost savings (the primary benefit of the rule) of about $444,000 – $459,000 per product. This savings represents the difference between the new costs of the process to submit a letter of self-determination and the old estimated costs that developers would have had to incur to meet Agency data requirements and to register the PIP. The annual number of PIPs based on sexually compatible plants created through biotechnology cannot be forecasted, so the Agency based annual and annualized cost savings estimates on an assumption that there would be one PIP that fit the exemption category per year for the next ten years. This estimate is meant to inform the public of the cost savings and their magnitude over time. The estimate avoids Agency conjecture about how many products would be registered in the absence of this exemption over time. The number of future PIPs based on sexually compatible plants created through biotechnology being developed will depend on the market for these products.

a. Growers.

Growers will have more tools to combat pest pressure because the proposed exemption might accelerate the development of new plant varieties containing exempt PIPs based on sexually compatible plants created through biotechnology that target those pests. Faster marketing of PIPs based on sexually compatible plants created through biotechnology will allow

the market to respond faster to changes in disease pressure and the emergence of resistance to existing pesticides, which can be important to growers. EPA anticipates that the proposed exemption for PIPs based on sexually compatible plants created through biotechnology will particularly encourage the development of PIPs based on sexually compatible plants created through biotechnology in minor crops. The limited acreage on which minor crops are cultivated makes it more difficult to recoup investment in research and development into new varieties, especially if regulatory costs are high.

b. The Agency.

Finally, the proposed exemption would also reduce the burden on the Agency to review applications for registration. By proposing to exempt those PIPs based on sexually compatible plants created through biotechnology due to low probability of risk and lack of unreasonable adverse effects in the absence of oversight, EPA will concentrate its regulatory efforts on other PIPs that may pose potential risks. Whereas the introduction of transgenes into a plant could result in the exposure of humans and the environment to a new substance or a previously known substance in a new way, the modifications associated with qualifying PIPs based on sexually compatible plants created through biotechnology are unlikely to result in novel exposures. Thus, concentrating regulatory efforts on PIPs with a higher potential of novel exposures is a more efficient use of EPA's resources.

B. What is the proposal to exempt residues of PIPs based on sexually compatible plants created through biotechnology from the requirement of a tolerance?

Pursuant to its authority under FFDCA section 408(e), 21 U.S.C. 346a(e), EPA is proposing to exempt from the requirement of a tolerance residues of pesticidal substances from PIPs based on sexually compatible plants created through biotechnology that meet the conditions

proposed for this exemption. The Agency believes that when the proposed conditions are met, there is a reasonable certainty that no harm will result from aggregate exposure to residues of these pesticidal substances from PIPs based on sexually compatible plants created through biotechnology, including all anticipated dietary exposures and all other exposures for which there is reliable information. The Agency believes the exemption criteria will ensure that the exempt PIPs would not result in exposures that are significantly different from what humans are currently exposed to in the food supply; therefore, the exemption would be safe in light of the history of safe exposures.

This proposed exemption is intended to address the second condition for exemption from FIFRA regulation under 40 CFR 174.21(b): the requirement for a tolerance exemption for the residues of PIPs intended to be produced and used in a plant used as food or feed. The proposed rule also includes a process through which developers of PIPs based on sexually compatible plants created through biotechnology submit either a self-determination letter or request for EPA confirmation that their PIP meets the criteria for exemption. That process is proposed at 40 CFR 174.90, and details of the process for and contents of an exemption eligibility determination submission are found in Unit VI.C. That unit also describes the circumstances in which submission of a separate determination for purposes of the FFDCA exemption for a PIP proposed for use in food or feed is required.

Given that the proposed exemption could potentially cover thousands of substances, a small fraction of which are known toxicants (for discussion see Unit VI.B.3.), the Agency is proposing to use certain guardrails to account for the rare instances in which residues of a pesticidal substance may reach levels in food or feed that are unsafe. First, EPA proposes a criterion for exemption under FFDCA that limits the presence of residues of the pesticidal

substance in the recipient plant. Specifically, residues of a pesticidal substance in plants used for food are allowed to be present only in the same plant tissues and developmental stages where such residues are found in a sexually compatible plant. Additionally, the levels of that pesticidal substance cannot exceed levels found in a sexually compatible plant, with the added limitation that those levels may not be injurious or deleterious to human health. In other words, if levels that are injurious or deleterious to human health are observed, the PIP and its residues would not be covered by the proposed exemption from the requirement of a tolerance. This approach is consistent with the existing exemption criteria for residues of a pesticidal substance from a sexually compatible plant, which also limit the levels of residues of exempt PIPs present in the food from that plant to those that are not injurious or deleterious to human health (40 CFR 174.508(c)). Second, under the proposed exemption for PIPs based on sexually compatible plants created through biotechnology, a developer may wish to request an exemption for residues of a pesticidal substance whose levels are commonly screened for in conventional breeding to ensure the safety of the food. In these instances, the developer of such a PIP would be required, as part of the exemption eligibility determination process proposed at 40 CFR 174.90, to describe how conventional breeding practices have been and will be performed on the recipient food plant to ensure that the levels of the pesticidal substance are not injurious or deleterious to human health. This is to affirm that PIPs based on sexually compatible plants created through biotechnology will be held to the same safety standards by the plant breeders as PIPs in plants created through conventional breeding. This requirement can be fulfilled by a developer with a confirmation that the product has been screened for acceptable levels of the pesticidal substance (e.g., generally accepted safe content for solanine in potatoes is 20-25 mg/100 g of fresh potato). Breeders have decades of experience developing new plant varieties and are familiar with the toxins that may

be produced by certain plants used for food and feed, e.g., by chemically analyzing the components of plants. Because PIPs based on sexually compatible plants created through biotechnology are equivalent to those substances found within plants that are sexually compatible with the recipient plant, these substances are not expected to be novel to breeders and the existing screening methods are similarly expected to remain effective. Third, as described further in Unit VI.C.1., residues of a PIP used in food or feed, which would include residues of a PIP based on a sexually compatible plant created through biotechnology, remain subject to the adverse effects reporting under 40 CFR 174.71 even after the residues have been exempted from the requirements of FFDCA. Therefore, upon learning of any adverse effects, which includes injurious or deleterious levels of the pesticidal substance in food or feed, EPA has the authority to reconsider whether the PIP and the residues of the PIP continue to meet the criteria for exemption. Further, as described in the preamble of the July 19, 2001 *Federal Register* notice implementing 40 CFR 174.71 (66 FR 37772; July 19, 2001), reports involving food or feed (i.e., those subject to enforcement under FFDCA) would be made to EPA, but EPA will share such reports with FDA. EPA and FDA will individually determine whether any action is necessary to protect the public health, and if so, what constitutes appropriate action based on their respective statutes (EPA - FIFRA, FDA - FFDCA). Therefore, 40 CFR 174.71 is a means of ensuring that EPA and FDA can address any potential hazard identified subsequent to self-determination or EPA confirmation that a PIP meets the requirements for exemption.

1. Proposed criteria and associated definitions.

Unit VI.A.2. outlines the scope of the FIFRA exemption proposal for PIPs based on sexually compatible plants created through biotechnology. The criteria and associated definitions discussed in that unit are equally relevant to the proposed FFDCA exemption for residues of

these PIPs for food and feed use. For example, the proposed definitions of "native allele," and "native gene" are discussed in greater detail in Unit VI.A.2. Also discussed in Unit VI.A.2. are the following phrases: "(1) The pesticidal substance is found in plants that are sexually compatible with the recipient plant; and (2) Limitations on expression profile." The proposed definition of "gene" is discussed in Unit V.A. Thus, the following considerations under the proposed FFDCA exemption refer to the concepts discussed in other parts of the exemption proposal when appropriate.

EPA is proposing criteria and supporting definitions that describe residues from PIPs based on sexually compatible plants created through biotechnology that the Agency expects to meet the FFDCA safety standard for establishing exemptions. This proposed exemption covers the residues of the pesticidal substance of those qualifying PIPs and would eliminate the need to establish a maximum permissible level in or on food and feed for these residues.

EPA's basis for its proposal is that the criteria of the exemption circumscribe a group of PIPs that will not result in novel exposures, dietary or otherwise. This analysis is based on the large body of knowledge about the history of safe use from foods containing these substances that have been consumed by humans for long periods of time. Because PIPs based on sexually compatible plants created through biotechnology are equivalent to those that could have been created through conventional breeding, plant breeders will retain their ability to ensure that the substances will be at safe levels for humans in the resulting food plant. EPA concludes that the potential is low that qualifying PIPs based on sexually compatible plants created through biotechnology introduce novel exposures (Unit VI.A.3.b.).

a. Large body of knowledge.

EPA relied on the large body of scientific literature that describes constituents of food from plants in sexually compatible populations (Ref. 37). EPA used scientific literature on the effect on humans of consumption of whole foods from plants generated from epidemiological studies (Ref. 24, 25, 27, 29, 31, 69, 70, 71, 72, 73) and animal model testing of the effects of either whole foods, or constituents from food, contained in these crops (Ref. 26, 28, 30, 74, 75, 76, 77) to draw conclusions on the potential risks to humans through the dietary (including drinking water) and residential (or non-occupational) route of exposure to these substances. EPA also considered scientific knowledge from a number of disciplines including genetics, plant physiology, phytopathology, toxicology, ecology, biochemistry, evolutionary biology, genomics, and plant breeding. Information from the field of plant physiology was considered regarding plant metabolism to evaluate the production of substances that may have pesticidal effects and conditions that may limit the plant's production of such substances, see Unit VI.B.1.c. and Unit VI.A.3.c. (Ref. 33). EPA considered information from the fields of biochemistry and toxicology, for example, to identify which substances in food from plants might pose a dietary risk (Ref. 37, 39, 78). The Agency also used experimental data derived from the science of phytopathology that characterize the pest resistance mechanisms in plants to understand the types of traits through which PIPs may confer resistance or tolerance to pests (Ref. 3, 79). The sciences of ecology and evolutionary biology were considered for information on genetic diversity, mutation, and reproductive isolation mechanisms in populations to understand the types of genetic changes that are likely to occur when plants interbreed in nature (Ref. 34). Plant breeding and genetics provided considerations to help describe the mechanisms of incompatibility and interbreeding, which aided EPA in determining when plants are likely to interbreed in nature. As discussed in greater detail in Unit VI.A.3.g., information from genomics and molecular biology

were considered to understand the ability of newer biotechnology techniques, such as those using genome editing techniques, to create traits equivalent to those found in conventionally bred plants (Ref. 35, 36).

Recommendations from several FIFRA SAP reports were considered in the development of the proposed exemption criteria for PIPs based on sexually compatible plants created through biotechnology, and to circumscribe the types of genetic modifications in the recipient plant that are unlikely to result in novel exposure to humans, dietary or otherwise (Unit II.C.3., Table 1).

b. Low potential for novel exposure.

All plants, including those commonly consumed as food, naturally contain pesticidal substances that confer pest resistance. Humans have for approximately 10,000 years selected and bred certain plants for food, feed, and fiber, that have these pesticidal characteristics. Humans are therefore familiar with and have been exposed to many plant-produced pesticidal substances and their residues, such as those that could be developed for use as PIPs based on sexually compatible plants created through biotechnology, in their diet and otherwise for millennia. Given that PIPs based on sexually compatible plants created through biotechnology are intended to represent a subset of substances present in plants that breeders are familiar with and that in many instances have been safely consumed by humans, EPA does not expect that these substances, or residues of these substances, would result in novel dietary exposures.

Several considerations for assessing the potential for novel risks for PIPs based on sexually compatible plants created through biotechnology are discussed in Unit II.C.3. in the context of the proposed FIFRA exemption. The concepts presented in that unit are equally relevant to the FFDCA safety assessment of residues of PIPs based on sexually compatible plants created through biotechnology that are used for food or feed.

Pesticidal traits have evolved in plant populations over time through the processes of mutation, selection, and genetic exchange with sexually compatible species (Ref. 47, 48). The ability to produce viable offspring is only possible in nature for organisms that are genetically similar and possess many traits in common. Traits, and the genetic material encoding them, can be passed through a sexually compatible plant population by breeding. The mixing of genetic material that occurs through breeding results in the members of a sexually compatible population having similar traits and similar genetic material. Due to the mixing of traits by mating, similar exposure scenarios are expected for food plants that are sexually compatible - in other words, substances in sexually compatible plants are expected to be similar and therefore, only substances that plant breeders are already familiar with are expected to be present in sexually compatible plants. This conclusion is consistent with the 1992, 1993, and 1994 FIFRA SAP reports that indicated that sexually compatible plants are more likely to have a common constitution than unrelated plants and thus movement of genetic material between sexually compatible plants is less likely to lead to novel exposures (Unit II.C.3., Table 1).

For agricultural plants, those defined as sexually compatible would also include existing plant cultivars, landraces, and breeding lines, as well as plant relatives that interbreed with crops but that are not currently used as agricultural plants. Plant breeders have for many years followed established practices to ensure safety when moving genes into agricultural varieties from nonagricultural relatives, particularly from inedible relatives, with no indication that substances resulting from these genes present higher levels of risk than those from genes moved only amongst agricultural varieties as long as those established practices are followed (Ref. 13, 14, 15, 16). Therefore, the likelihood that the inclusion of nonagricultural varieties as potential source plants would lead to unsafe dietary exposures from residues of PIPs based on sexually

compatible plants created through biotechnology is low.

Genetic diversity is created over time and EPA proposes to capture some of the ongoing diversification not identified in existing native genes or native alleles through the inclusion of novel changes resulting in the differential expression of existing genes, so long as no novel substance is produced and the substance is not produced in different tissues or at different developmental stages than those found in a sexually compatible plant. Modifications that lead to differential expression of a substance are not expected to result in levels that exceed the boundaries of the natural variation found in sexually compatible plants due to physiological constraints that are related to energy expenditure (further discussed in Unit VI.B.1.c. and Unit VI.A.1.c.). The potential for novel dietary exposures to occur with the differential expression of existing genes, or the movement of native genes and native alleles among sexually compatible plants, is therefore low, because no substance novel to plants that are sexually compatible with the recipient plant will be produced, nor will the substance be found in tissues or developmental stages at levels, in which it is not currently found.

c. Low potential for levels of PIPs based on sexually compatible plants created through biotechnology to exceed those found in sexually compatible plants.

EPA has evaluated whether there are likely to be quantitative changes in expression levels of PIPs based on sexually compatible plants created through biotechnology that may pose dietary risks. As discussed later in this unit, EPA has determined that the probability is low because the highest levels of pesticidal substances likely to be expressed by qualifying PIPs based on sexually compatible plants created through biotechnology is not likely to be significantly different from those that humans are currently exposed to in the food supply. To codify this principle into EPA's regulatory text, EPA is proposing an exemption criterion in

which the level of expression of PIPs based on sexually compatible plants created through biotechnology is bound by the upper limit of expression of the pesticidal substance observed in sexually compatible plants. By limiting the level of expression that qualifies for an exemption in this way, EPA can ensure that the exposures fall within the normal historical range of exposures with which plant breeders have experience limiting to ensure safe exposures when introduced into food plants.

An analysis discussing the likely range of expression of PIPs in sexually compatible plants was presented in an EPA issue paper, entitled: "FIFRA: Benefit and Environmental Risk Considerations for Inherent Plant-Pesticides." A summary of that analysis is presented in Unit VI.A.3.c. The factors that influence the determination of low probability of risk under FIFRA that are discussed in that unit are equally relevant to the FFDCA safety assessment of residues of those same PIPs in food or feed. Relevant considerations summarized in that unit include: (1) The level of production of substances normally varies among sexually compatible plants because of differences in potential to express a substance and environmental conditions; (2) Physiological and practical considerations limit the expression levels of PIPs based on sexually compatible plants created through biotechnology; (3) Humans have been and are currently exposed to the range of levels of substances that might be used as PIPs based on sexually compatible plants created through biotechnology.

Moreover, in varietal development, plant breeders assess the new cultivar for food safety, based in part on knowledge of and familiarity with the characteristics of agricultural plants in the relevant sexually compatible populations (Ref. 6, 37). Because PIPs based on sexually compatible plants created through biotechnology represent a subset of substances already present in related plants, the procedures routinely used in agriculture and food processing would

continue to be efficacious in identifying these substances, and levels of these substances, in new food plant varieties.

Although hundreds of new plant varieties enter the market each year within the past 70 years, conventional plant breeding has recorded very few instances of plant varieties causing food safety problems (Ref. 37, 80). EPA believes this same demonstrated record of safety can be applied to the pesticidal substances produced by these plants. Therefore, the Agency considers it highly unlikely that residues of a PIP based on a sexually compatible plant created through biotechnology would occur in or on food or feed at levels that are hazardous. To account for the rare instances in which a substance may reach levels that are unsafe, EPA is proposing as a criterion for exemption that residues of the pesticidal substance are only present in tissues and developmental stages identified in a plant that is sexually compatible with the recipient food plant, and do not exceed levels found within that plant, as long as those levels are not injurious or deleterious to human health. If levels that are injurious or deleterious to human health are observed, the PIP and its residues would not be covered by the proposed exemption from the requirement of a tolerance. In failing to meet the FFDCA requirements for exemption, the PIP would similarly fail to meet the exemption requirements under FIFRA.

In conclusion, EPA considered the potential variability of expression levels of PIPs based on sexually compatible plants created through biotechnology and whether such variations would be hazardous if they were to be present in the food or feed supply. EPA concluded that although variations in the production of plant substances will occur in response to environmental conditions, there are physiological and practical considerations that limit the expression level, and thus the abundance of a particular substance in plants that are sexually compatible. By limiting the expression of PIPs based on sexually compatible plants created through

biotechnology to not exceed levels that are found in sexually compatible plants, EPA believes that breeders will be able to ensure that exposures fall within the normal historical range of exposures that have proved to be safe through conventional breeding.

2. Dietary risk evaluation.

For chemical pesticides, EPA's dietary risk evaluation relies on data generated by testing in laboratories using representative animal models to estimate acute, subchronic, or chronic hazard endpoints, e.g., acute toxicity, carcinogenicity, and developmental toxicity. Conclusions from animal models are used to assess dose-response and describe such endpoints for potential human hazards. Other information, including residue data and information generated by use of mathematical models, are used to develop human exposure estimates. These exposure and hazard components are combined to quantify the potential risk associated with the pesticide's use and to determine the appropriate maximum residue levels of the chemical in or on food or feed, i.e., to set the numerical tolerance. Uncertainty factors are often used in the risk assessment to account for extrapolation from animal models to human toxicity. If the substance is found to be safe, the Agency may issue a tolerance or, as proposed here for qualifying PIPs based on sexually compatible plants created through biotechnology, an exemption from the requirement of a tolerance for the pesticide chemical residues. EPA described the information base typically used to assess the potential risks and safety of PIPs at a public symposium held in September 2016. The materials developed for this symposium are available on *http://www.regulations.gov* in Docket ID No. EPA-HQ-OPP-2016-0427 and on EPA's website at *https://www.epa.gov/pesticides/public-symposium-regulation-plant-incorporated-protectants-rebroadcast-live-webcast*.

In some cases, the use of animal model testing may not be required to support a safety finding for a pesticide chemical residue. For example, for PIPs that are already part of the food supply but moved through the use of biotechnology between two distantly related food plant species (i.e., those that are not sexually compatible and could not have been moved through conventional breeding), EPA has used various forms of information aside from animal testing to assess the safety of PIP residues. These included the open scientific literature to understand the characteristics of the PIP itself as well as the biology of the source plant from which the PIP is derived and the recipient plant in which the PIP will be produced and used. Similarly, in performing the assessment for the proposed tolerance exemption for PIPs based on sexually compatible plants created through biotechnology, the Agency is assessing the substances present in these plants in the context of the history of human consumption of the whole food, and animal model testing of the effects of either whole foods, or constituents from food, contained in these crops (Unit VI.B.1.a.). EPA's conclusion that qualifying PIPs based on sexually compatible plants created through biotechnology would be safe for human consumption is based on this information. EPA considered that appropriate processing procedures are widely known and are routinely used by consumers and companies involved in food production and processing in the preparation of food containing residues that are the subject of this proposed exemption, including those foods that require specific processing and/or preparation steps in order to be safely consumed B.3.). Importantly, the efficacy of the food preparation techniques, as well as dietary avoidance strategies, are expected to apply equally to food containing residues of PIPs based on sexually compatible plants created through biotechnology, since residues of those pesticidal substances are a subset of substances already present in related food plants. Similarly, the plant breeding practices that are routinely employed in selecting and developing new plant varieties,

such as chemical analysis and visual analysis, are not expected to be affected by this proposed exemption. As a result, the residues are not expected to pose any risk that differs from what people already are exposed to in the food supply.

EPA considered health risks to the general population, including infants and children. Residues of pesticidal substances in or on food or feed from PIPs based on sexually compatible plants created through biotechnology that meet the proposed criteria for exemption would not be new to the food supply, as they are a subset of substances already present in related plants. Accordingly, this proposal should not change anything about the way that children, and to some extent infants, are exposed to substances already found in food that are identical to residues of PIPs based on sexually compatible plants created through biotechnology. EPA's risk assessment also included subgroups as part of the general population, i.e., reflecting differences in diet due to the influence of culture, and allowed for consumption pattern differences of such subgroups.

a. Dietary consumption patterns.

EPA considered the available information on the varying dietary consumption patterns of consumers and major identifiable consumer subgroups as it pertains to residues of pesticidal substances from PIPs based on sexually compatible plants created through biotechnology. The consumption of food from plants is part of a balanced and varied diet (Ref. 81). For purposes of this proposed exemption, EPA considered a normal diet to be balanced and varied and to include food from a variety of sources. It does not include plants or plant parts consumed in times of deprivation, for religious reasons, in substance abuse, or by accident. Humans have been consuming food containing pesticidal substances produced by sexually compatible plants for long periods of time. It is not anticipated that this proposed exemption from the requirement of a tolerance, should it be finalized, will affect current consumption patterns of food from crop

plants by consumers or major identifiable consumer subgroups, and thus no differences in exposure patterns are anticipated.

b. Validity, completeness, and reliability of available data.

EPA considered the validity, completeness, and reliability of the available information on human consumption of food containing substances that would be identical to the expected residues of pesticidal substances from PIPs based on sexually compatible plants created through biotechnology, including the extensive history of humans safely consuming foods from plants containing these substances, epidemiological studies of human dietary assessments and animal model testing, as well as information from the disciplines of genetics, molecular biology, plant physiology, phytopathology, toxicology, ecology, biochemistry, evolutionary biology, genomics, and plant breeding (Unit VI.B.1.a.). EPA concluded that this information was valid, complete, and reliable, and adequately addressed the issues of hazard and exposure with regard to residues of pesticidal substances from PIPs based on sexually compatible plants created through biotechnology in or on food or feed.

3. Toxicological profile.

EPA considered whether toxic effects could be associated with any pesticidal substances that developers might wish to use as PIPs based on sexually compatible plants created through biotechnology and that might be residues in or on food or feed (Ref. 6). The examination led EPA to conclude that, since the vast majority of substances in plants that are used for food are not toxic, any of these nontoxic substances, should they be used as PIPs based on sexually compatible plants created through biotechnology, would not present any toxic effects.

Plants produce hundreds of thousands of substances of which only about 200 have been identified as potential toxins in food plants, and only 10% of those substances (about 0.01% of

all substances) may pose a dietary risk when consumed as part of a normal diet (Ref. 37, 82, 83). One example is the glycoalkaloid solanine, which is commonly biosynthesized in potatoes and to some extent eggplant and peppers (Ref. 6). Solanine poisoning is very rare. However, in large doses it can cause effects such as gastrointestinal tract irritation and drowsiness. Solanine imparts a bitter taste to the tuber, and at high concentrations can even leave a persistent irritation and burning sensation on the tongue, both of which may to some extent deter consumption. Potatoes are bred and monitored in the United States to ensure that they produce only low levels of solanine.

There are several factors that could have contributed to the relatively low number of toxins in food plants. In crop development, low toxicant abundance has been a desired trait to increase usability of a particular plant as a source of nutrition and to enhance its palatability (Ref. 4, 37). Further, the risk of toxins that may be present in a particular food crop appears to be well known, and methods of processing exist to reduce the potential for toxic effects (Ref. 37). For example, as part of the development and characterization of new plant varieties, plant breeders use methods such as gas and/or liquid chromatography coupled with mass spectrometry to identify and quantify toxins in food plants and use this information to identify and remove new varieties from the development pipeline that contain potentially harmful levels of these substances. Over the past 50 years, the sensitivity of some metabolic profiling techniques has increased over 100,000-fold, enabling the detection of exceedingly small amounts of these substances (Ref. 37). As a result, the majority of toxicants in food plants are already known and plant varieties can be screened for their presence and removed from the market if necessary. In this context it is relevant to note that no newly released plant variety exhibited any previously unknown food or feed hazard (Ref. 37, 80).

Because PIPs based on sexually compatible plants created through biotechnology are a subset of those PIPs found in related plants, these substances are not novel to plant breeders. Therefore, the efficacy of the existing monitoring, processing, and preparation methodologies that have been and are being used to produce food safe for consumption is expected to be equally effective at screening foods that would contain PIPs based on sexually compatible plants created through biotechnology. For the reasons described in Unit VI.B.1.b., EPA expects that PIPs based on sexually compatible plants created through biotechnology do not pose novel exposures (dietary or otherwise) compared to pesticidal substances present in sexually compatible plants. Furthermore, EPA expects that the levels of PIPs based on sexually compatible plants created through biotechnology have a low potential to exceed levels found in sexually compatible plants (Unit VI.B.1.c.) and codifies these levels in the proposed exemption criteria.

4. Cumulative effects from substances with a common mechanism of toxicity.

FFDCA section 408(b)(2)(D)(v) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." This factor is also relevant when considering whether to establish an exemption from the requirement of a tolerance (21 U.S.C. 346a(c)(2)(B)).

As discussed in Unit VI.B.3., EPA recognizes that there are toxicants of plant origin that may be part of the human diet, which could theoretically be used as PIPs based on sexually compatible plants created through biotechnology and which may cause adverse effects. EPA has considered available information on the cumulative effects of such residues and other substances that have a common mechanism of toxicity and that may be developed as PIPs based on sexually compatible plants created through biotechnology. EPA also considered whether the cumulative

expression (i.e., expression of the PIP across all plants) would result in an adverse effect. Because the PIP based on a sexually compatible plant created through biotechnology could have otherwise been created through conventional breeding, and by extension would not be novel to plant breeders, EPA does not consider that the cumulative expression of a PIP based on a sexually compatible plant created through biotechnology would pose a higher risk than what is currently possible through conventional breeding.

For the reasons discussed in Units VI.B.1.a. through c., any potential cumulative effects from PIPs based on sexually compatible plants created through biotechnology are not expected to be quantitatively different from those present in the current food supply and the presence of these substances and their residues has historically been safe.

5. Aggregate exposures of consumers including non-occupational exposures.

EPA considered the available information on the aggregate exposure of consumers to the residues of PIPs based on sexually compatible plants created through biotechnology. EPA examines exposure through the dietary route (including drinking water), and exposure in the residential non-occupational setting in greater detail in the following units (Unit VI.B.5.a. through e.).

a. Dietary exposures from food.

Dietary exposure is the most likely route of exposure to PIPs based on sexually compatible plants created through biotechnology as these pesticidal substances are contained within plants consumed as food. As described in this preamble at Unit VI.B.1.a., a large knowledge base and experience exists for the residues that are subject of this proposed exemption, including information on human dietary exposure. Information from all of these sources can be used in evaluating the safety of residues of PIPs based on sexually compatible

plants created through biotechnology, as food from a plant engineered to contain such a PIP is comparable to the situation presented by the natural whole food from that plant prior to introducing the genetic modification: No substances new to the sexually compatible plant population would be introduced, and the introduced substances would be consumed as part of the whole food.

The exemption criteria prohibit the introduction of substances that are novel to the sexually compatible plant population and, as discussed earlier, nothing about the PIP would alter the existing mechanisms for breeding, processing or preparing the food. Thus, the Agency expects any exempt PIPs would be consumed as part of the whole food in the same manner as existing foods currently in the food supply and that plants containing residues of these PIPs would be subject to the same procedures plant breeders rely on to ensure the safety of food. There is no evidence in the many studies performed on the relationship of diet to health that food containing substances from sexually compatible plants, when properly processed and prepared, has resulted in adverse health effects (Unit VI.B.1.a. through c.). The Agency believes this assumption is supported by the record of safety of the food products from plants in sexually compatible populations. Although hundreds of new varieties come on the market each year (Ref. 84), breeding of plants in sexually compatible populations has recorded very few instances of exposures to substances that are not safe in food. Further, no previously unknown food hazard has been observed in new plant varieties developed through plant breeding (Ref. 37, 80).

The primary exposure consideration associated with the pesticidal chemical residues that are the subject of this proposed exemption is whether substances that might be harmful at higher concentrations (or in different tissues or stages) are likely to be present in food from sexually compatible plants at such concentrations. EPA considered the probability of variations in levels

of PIPs based on sexually compatible plants created through biotechnology, and whether such variations would be hazardous if these PIPs were to be present in the food supply (Unit VI.B.1.c.). EPA concluded that, based on biological and agronomic considerations, any variations in the levels of PIPs based on sexually compatible plants created through biotechnology is not expected to exceed the levels of these substances currently present in the food supply, which has been determined to be safe. This principle is also codified in EPA's proposed regulatory text in which the level of expression of a PIP based on a sexually compatible plant created through biotechnology is bound by the upper limit of expression of the pesticidal substance observed in sexually compatible plants and that it can only be present at levels that are not injurious or deleterious to human health.

A second exposure consideration is whether this proposed exemption will affect the ability of individuals with food sensitivities to manage these sensitivities. Individuals with food sensitivities, including food allergies, generally avoid foods from plants that they are sensitive to. This proposed exemption, if finalized, would not affect the efficacy of this strategy of avoidance because the proposed exemption will not affect the ability of individuals to recognize and avoid foods they are sensitive to. For example, the ability of persons who have the Mediterranean form of the inherited Glucose-6-phosphate dehydrogenase (G6PD) deficiency to manage their disease by not consuming fava beans or foods made with fava beans will not be affected. The substances in fava beans that can cause hemolytic anemias in such persons would be exempt only if they are used in fava bean plants and plant varieties that interbreed with fava beans; a population of plants in which such substances normally occur (Ref. 85).

In conclusion, qualifying PIPs based on sexually compatible plants created through biotechnology represent a subset of substances already present in related plants. Therefore,

should residues of these substances be present in or on food derived from plants, EPA does not expect them to have any meaningful impact on the already existing dietary exposure profile for these residues and thus risk from dietary exposure to such residues in or on food would be low. Moreover, as an additional measure of safety for residues of qualifying PIPs, the pesticidal substance can only be present at levels that are not injurious or deleterious to human health.

b. Residential, non-occupational exposure.

Residues of qualifying PIPs based on sexually compatible plants created through biotechnology may be present in plants grown residentially for consumption. Consequently, EPA examined the potential for non-occupational exposures to these substances in the sections for dermal and inhalation exposure in sections of Unit V.B.5.d. and e.

c. Dietary exposure from drinking water.

Dietary exposure through drinking water is considered unlikely. The substances in plants or parts of plants, including residues of PIPs based on sexually compatible plants created through biotechnology, are produced and used inside the living plant itself. As such, the residues are part of the tissue of the plant. When the plant dies or a part is removed from the living plant, microorganisms colonizing the tissue immediately begin to degrade it, using the components of the tissue, including any residues that are the subject of this proposed exemption, as building blocks for making their own cellular components or for fueling their own metabolisms. The residues that EPA is proposing to exempt in this action are subject to the same processes of biodegradation and decay that all biotic materials undergo. This turnover of biotic materials in nature through a process of biodegradation is expected to occur in rapid fashion and is likely to preclude these residues from persisting in the environment long enough to reach the drinking water supply (Ref. 40). There is no indication that plant biotic materials, including the residues

that are the subject of this proposed exemption, are resistant to biodegradation. Even if residues were to reach surface waters, through pollen dispersal or parts of the plants (leaves, fruits etc.) falling directly into bodies of water, they are still subject to microbial degradation and are unlikely to present anything other than a negligible exposure in drinking water drawn either from surface water or ground water sources. Importantly, PIPs based on sexually compatible plants created through biotechnology represent a subset of substances already present in related plants. Therefore, should these residues be present in drinking water, they are not expected to meaningfully alter the already existing pattern of exposure to these residues and thus EPA expects risk to be negligible.

d. Dermal exposure.

Although a potential for dermal exposure may exist, EPA expects such exposure to be negligible because PIPs based on sexually compatible plants created through biotechnology are present in the plant tissue (Ref. 60). In some cases, residues of PIPs based on sexually compatible plants created through biotechnology may be present in sap or other exudates from the plant and thus may present some limited opportunity for dermal exposure to persons coming physically into contact with the plant or raw agricultural food from the plant, e.g., during food preparation (see also Unit VI.A.3.e.). Although contact dermatitis can occur from such exposure (Ref. 60, 86), these reactions are generally mild, of a self-limiting nature, or self-diagnosed and treated. For those substances that possess to some degree properties that might allow some penetration of the skin, the potential amount passing through the outer epidermal layer of the skin (epidermis) is likely to be low (Ref. 60).

Furthermore, most of the substances that could be the subject of this proposed exemption are unlikely to pass through the skin to affect other organ systems or elicit allergic sensitization

(Ref. 60, 61, 86, 87). Importantly, those substances that do possess properties that allow some penetration of the skin represent a subset of substances already present in related plants and would therefore not be expected to alter the already existing exposures to plant proteins or other plant substances through handling of the plant containing these substances. Therefore, EPA does not expect novel hazards or exposures from residues of the substances involved and thus these PIPs are expected to represent a low potential of quantitatively different dermal exposures; therefore, risks from dermal exposures are expected to be low.

e. Inhalation exposure.

Although a potential for inhalation exposure may exist, EPA expects such exposure also to be negligible because PIPs based on sexually compatible plants created through biotechnology are contained within plant cells, which essentially eliminates this exposure route, or reduces this exposure route to negligible levels (Ref. 60). However, residues of PIPs based on sexually compatible plants created through biotechnology may in some cases be present in pollen and other agricultural dust and some individuals, e.g., those living or working in close enough proximity to farms, nurseries or other plant-growing areas, may be exposed to wind-blown pollen, or through visiting such areas may be exposed, through inhalation, to the pollen. The most likely impact of pollen exposure is rhinitis, or inflammation of the mucous membranes lining the nose, resulting in symptoms like nasal congestion, sneezing, itching, post-nasal drainage, and runny nose.

On a per person basis, the potential amounts of pollen involved in these exposures are likely to be low and residues of the pesticidal substance will not in every case be present in the pollen. Importantly, pollen characteristics (e.g., wind versus insect dispersal, amount produced) are often maintained within plant families and, therefore, residues of PIPs based on sexually

compatible plants created through biotechnology, which are found among sexually compatible plants, should not alter already established characteristics of any particular plant species. This proposed exemption will not change current exposures, nor affect strategies for dealing with reactions to PIPs based on sexually compatible plants created through biotechnology that may be aero-allergens or irritants (Ref. 60). Thus, EPA concludes that risk from inhalation exposure to residues of PIPs based on sexually compatible plants created through biotechnology is low.

6. Other considerations.

Other considerations for EPA's safety finding under the FFDCA include the sensitivities of population subgroups, endocrine effects, and special consideration for risks to infants and children.

a. Sensitivities of subgroups.

EPA considered available information on the sensitivities of subgroups as it pertains to residues of qualifying PIPs based on sexually compatible plants created through biotechnology. In performing its assessment, the Agency considered that the diet includes all of the food items that are customarily eaten by human populations or population subgroups. As discussed in this preamble, this proposed exemption will not affect the current pattern of exposure to residues that are the subject of this proposed exemption because the substances at issue are equivalent to substances present in sexually compatible plants and are limited in their level of expression to those observed in sexually compatible plants. Relatedly, the expression pattern of these substances (timing and location of the expression) are limited to those found in sexually compatible plants through the proposed criteria. Individuals recognize and are familiar with the plant-derived food they consume, (e.g., based on prior experience of consumption) and would avoid consuming foods containing substances they know they are sensitive to (Ref. 37, 88, 89).

Because the exposure pattern to these foods will not be affected by this proposed exemption, the efficacy of the current strategy whereby sensitive individuals or subgroups of sensitive individuals recognize and avoid certain foods would not similarly not be affected (Ref. 88, 89). Thus, the Agency does not expect any subgroup to be adversely affected by the proposed exemption.

b. Estrogenic or other endocrine effects.

Certain food plants, e.g., soybeans, contain estrogen mimics, termed phytoestrogens. Such phytoestrogens are currently being consumed by humans in food derived from plants and are part of the extensive history of safe human consumption of food from plants. Although the Agency considers use of these phytoestrogens as PIPs to be unlikely, EPA cannot rule out the possibility that such phytoestrogens could be developed as PIPs based on sexually compatible plants created through biotechnology. Based on available information concerning levels of phytoestrogens that must be consumed before effects can be seen (Ref. 90), the natural limitations of gene expression (Unit VI.A.3.c.), and the limitations the Agency is proposing on the levels and expression pattern of these substances at 40 CFR 174.541(b), EPA expects that this exemption, as proposed, will not result in levels of phytoestrogens in foods that would be quantitatively different from those currently being safely consumed.

c. Infants and children.

FFDCA section 408(b)(2)(C) provides that EPA shall assess the risk of pesticide residues based on available information about infants' and childrens' consumption patterns, special susceptibility to pesticide chemical residues, and the cumulative effects. EPA's evaluation of these factors is presented in the following units (Unit VI.B.6.c.i. through iii.).

In addition, this section of the FFDCA requires that, in the context of threshold effects,

EPA apply an additional tenfold margin of safety to take into account potential pre- and postnatal toxicity and completeness of the toxicity and exposure databases with respect to infants and children. This safety factor is most relevant when the Agency conducts a quantitative risk assessment upon identifying threshold effects of concern and employs various uncertainty factors, including this safety factor, to ensure an appropriate margin of safety in its risk analysis.

For residues of PIPs based on sexually compatible plants created through biotechnology, EPA has concluded that consumption of food containing residues of PIPs based on sexually compatible plants created through biotechnology is safe for infants and children, and that a margin of safety need not be proposed for these residues in food. EPA based its assessment of exposure and toxicity upon the information base described in this preamble in Unit VI.B.1.

i. Dietary consumption patterns.

EPA considered available information on the dietary consumption pattern of infants and children as it pertains to residues of PIPs based on sexually compatible plants created through biotechnology. The range of foods consumed by infants and children is in general more limited than the range of foods consumed by adults. Most newborns rely on milk products for nutrition, although some infants are fed with soy-based products. Soy-based products may contain residues that are the subject of this proposed exemption. Infants begin as early as 4 months of age to consume specific types of solid foods, including foods from plants that may contain residues that are the subject of this proposed exemption. Later on, apart from processing to facilitate swallowing, the diets of toddlers begin to be based on foods consumed by the general adult population albeit in different proportions. As infants and children mature, more and more of the foods consumed by adults become part of their diets and the relative proportions of the different types of food consumed change to more closely resemble an adult diet.

Foods that may contain residues that are the subject of this proposed exemption are part of a normal diet. They have been consumed by infants and children over long periods of time. The likelihood that exposure as part of a normal diet to these substances could lead to harm to infants and children is low. As the diets of humans change from infancy through childhood and into adulthood, there is some possibility that the amount of foods that contain residues that are the subject of this proposed exemption being consumed may change, with those consuming the greatest amounts of plant-based foods being the most exposed to substances that may be subject of this proposed exemption. There is no evidence, however, that such changes are likely to result in disproportionately high consumption of these residues in comparison to the general population. Thus, there is no evidence that any exposures would be different from those currently in existence. The evidence suggests that consumption of foods containing residues from PIPs based on sexually compatible plants created through biotechnology, including changes in exposure (i.e., relative proportions of the different types of food consumed from infancy through childhood and into adulthood) is highly unlikely to lead to any harm (Units VI.B.1. through 5.).

ii. Special susceptibility.

EPA considered available information on the potential for special susceptibility of infants and children, including prenatal and postnatal toxicity, to residues of qualifying PIPs based on sexually compatible plants created through biotechnology. The substances that are the subject of this proposed exemption occur in the normal diet, and there is no evidence that exposure to such residues, as components of food, present a different level of dietary risk for infants and children.

iii. Cumulative effects of residues with other substances with a common mechanism of toxicity.

EPA examined the available information on the cumulative effect of residues of PIPs

based on sexually compatible plants created through biotechnology, as well as other substances in food that may have a common mechanism of toxicity with these residues, and considered effects on infants and children (Unit VI.B.4.). Food from sexually compatible crop plants is being safely consumed by humans, including infants and children, either directly or indirectly in products such as meat and milk that are derived from animals that consume forage and other crops, e.g., corn and other grains. Considering the history of safe consumption and the information base described in Unit VI.B.4., EPA has not found that substances in food from plants share common mechanisms of toxicity with other substances.

d. Safety conclusion.

Based on the information discussed in this preamble and in the associated record, EPA preliminarily concludes that when the proposed conditions are met, there is reasonable certainty that no harm will result from aggregate exposure to residues of PIPs based on sexually compatible plants created through biotechnology, including all anticipated dietary exposures to humans for which there is reliable information. This preliminary finding is based on the Agency's determination that the proposed exemption criteria would only exempt PIPs that share relevant characteristics with PIPs already found in sexually compatible plants, thereby ensuring that residues of these PIPs do not pose different risks to humans. Specifically, the proposed exemption only applies to substances already found in plants that are sexually compatible with the recipient food plant, that are present in tissues and developmental stages identified in those plants, and whose expression does not exceed levels that are found within those plants. Moreover, as an additional measure of safety, the exemption specifically excludes those residues of PIPs from the exemption that are present in the recipient food plant at levels that are injurious or deleterious to human health. The safety determination for PIPs based on sexually compatible

plants created through biotechnology is based on a large body of knowledge about the history of safe use from foods containing residues of PIPs that are present in plants and EPA's assessment of scientific literature that describes constituents of food from plants in sexually compatible populations. To develop the proposed exemption criteria for PIPs based on sexually compatible plants created through biotechnology, and to circumscribe the types of genetic modifications in the recipient plant that are unlikely to result in novel exposure to humans, dietary or otherwise, EPA relied on recommendations from several FIFRA SAP reports and considered information from the public literature to understand the ability of newer biotechnology techniques to create traits equivalent to those found in sexually compatible plants.

e. Analytical enforcement methodology.

Before issuing an exemption from the requirement of a tolerance, the FFDCA requires an analytical method for detecting and measuring the levels of the pesticide chemical residue at issue in food, unless the Administrator determines that there is no need for such a method and explains the reasons for that determination in the rulemaking establishing the exemption (21 U.S.C. 346a(c) (3)). In the case of a reversal of an exemption decision, established analytical methods could be critical to enable detection of the affected crop, e.g., should a recall of foods be necessary. To meet the proposed exemption criteria at 40 CFR 174.21(d), a developer is likely to already be in possession of the analytical methods that can be used for the detection of either the genetic material or the gene product associated with the PIP. For example, to provide the nucleic acid sequence information of the PIP as part of the exemption eligibility process, developers may use several oligonucleotide primers for gene sequencing. These primers can similarly be used for the specific detection of the PIP in the food plant using standard PCR methods. Conversely, in those instances in which primers are not already available, the information provided on the

nucleic acid sequence of the PIP is expected to be sufficient to promptly design oligonucleotide primers *de novo*. Therefore, EPA does not find it necessary to require submission of analytical methods for the detection in plants of PIPs based on sexually compatible plants created through biotechnology.

C. What are the Proposed Exemption Eligibility Determination Procedures and Requirements of 40 CFR Part 174, Subpart E?

EPA proposes to use currently reserved Subpart E of 40 CFR part 174 for a proposed exemption eligibility determination process related to the proposed exemptions. Within that subpart, EPA proposes adding four sections: one to describe the process for determining eligibility for an exemption, one to describe the general submission process for a self-determination letter, one to describe the general submission process for EPA confirmation, and one to describe the information requirements specific to PIPs based on sexually compatible plants created through biotechnology. These additions are necessary because EPA is proposing to make the exemption of PIPs based on sexually compatible plants created through biotechnology contingent upon notifying EPA prior to a PIP being brought to market through a self-determination letter and/or by seeking EPA confirmation that a PIP meets the exemption criteria (options described in Unit VI.C.1.).

The proposed exemption eligibility determination process will allow the Agency to maintain a record of the PIPs that meet the criteria for exemption. This record will aid in inspections conducted by the Agency to ensure compliance and to confirm that PIPs in the food supply do indeed meet the standard of safety as defined by the exemption criteria. Also, if it were determined based on new information that a PIP was not eligible for exemption, such a record would help inform EPA and the FDA of the most appropriate steps to protect public health

(including enforcement). As described in Unit VI.A.4., with the proposed exemption eligibility determination process, exempting PIPs based on sexually compatible plants created through biotechnology has an estimated incremental cost saving of about $444,000 – $459,000 per product, compared to traditional registration, due to reductions in PRIA fees and data generation.

1. Proposed section for determining the eligibility of a PIP to qualify for exemption.

The Agency is proposing a new provision in Subpart E, 40 CFR 174.90, entitled "Determining eligibility for exemption." This provision states that developers have two, non-mutually exclusive options to notify EPA that their PIP meets the exemption criteria: (1) submit a self-determination letter that a PIP meets the exemption criteria, and (2) seek EPA confirmation that a PIP meets the exemption criteria. EPA confirmation can be sought instead of, in conjunction with, or subsequent to the submission of the self-determination letter. EPA believes that such a confirmation holds multiple potential benefits, including reduced barriers to international trade, increased public confidence in product safety, and affirmation for the developer that it has correctly determined that the PIP meets the criteria for exemption.

The provision further explains the relationship between the EPA confirmation processes and a letter of self-determination. Specifically, if a developer chooses to request EPA confirmation in accordance with 40 CFR 174.93 in conjunction with or subsequent to submitting a self-determination letter in accordance with 40 CFR 174.91, the exemption is effective from the time at which the company receives confirmation of submission of the self-determination letter. The exemption remains effective if EPA affirms the developer's determination that the PIP meets the exemption criteria and the self-determination is superseded by EPA's written confirmation in response to the confirmation request. However, if at any time after submission of the self-determination, EPA determines that the PIP was not eligible for exemption under this

proposed rule, the exemption will not have applied, and EPA may take enforcement against that product to ensure compliance with FIFRA. Similarly, FDA may take enforcement action if an incorrect self-determination was made by a developer of a PIP in a plant used for food or feed. As indicated in Unit VI.C.2., the developer is responsible for ensuring the accuracy of its self-determination.

Alternatively, in instances in which no prior self-determination has been provided to the Agency in accordance with 40 CFR 174.91 and the developer submits a request for confirmation to the Agency, the exemption applies only once EPA provides written notice to the developer confirming that the PIP meets the criteria for exemption. EPA reserves the right to assess or revisit at any time whether a PIP meets, or has met, the criteria for exemption regardless of whether the developer requests EPA confirmation. In particular, as exempt PIPs are still subject to 40 CFR 174.71, upon learning of any adverse effects (e.g., injurious or deleterious levels in food), EPA has the authority to evaluate whether the PIP still meets the criteria for exemption. As described in the preamble of the July 19, 2001 *Federal Register* notice implementing 40 CFR 174.71 (66 FR 37772; July 19, 2001), reports involving food or feed (i.e., those subject to enforcement under FFDCA) would be made to EPA, but EPA will share such reports with FDA. EPA and FDA will individually determine whether any action, including the possibility of enforcement, is necessary to protect the public health or the environment, and if so, what constitutes appropriate action based on their respective statutes (EPA - FIFRA, FDA - FFDCA). Therefore, 40 CFR 174.71 is a means of ensuring that EPA and FDA can address any potential hazard identified subsequent to self-determination or EPA confirmation that a PIP meets the requirements for exemption.

The provision also outlines instances in which an exemption determination can be

extended to subsequent variations of the PIP. For a PIP based on a sexually compatible plant created through biotechnology, EPA is proposing that a determination that the PIP meets the exemption criteria would be required for each modified gene and plant species combination, made either by the developer through a self-determination letter or by EPA through a confirmation request. However, EPA is aware that a plant species can comprise multiple varieties and does not intend for the PIP in each variety to require its own submission if a developer creates the same modification in different varieties. In this case, that developer would need to notify EPA only for the first modification in that species. The specific circumstances when an exemption determination is not required when modifying additional varieties of a plant species differ slightly depending on whether the developer is creating the same substance with the modification (e.g., native allele) or whether the developer is creating the same phenotype via a novel mutation. If the developer is creating the same substance with the modification (e.g., native allele) in other varieties, then subsequent notifications are not required so long as no additional modifications were made to the regulatory region. If the developer is creating the same phenotype by modifying the regulatory region via a novel mutation in other varieties, then subsequent notifications are not required. For example, if a developer modifies an existing gene in a tomato variety to create a native allele, this would require a determination; however, if the developer subsequently creates the same native allele in another tomato variety, the developer would not be required to submit a second determination request for the additional variety. Similarly, if a developer creates a differentially expressed gene, subsequent modifications in other varieties would not require a determination if the developer targets the same nucleic acid sequence (e.g., uses a guide RNA to target the same location in a gene in a CRISPR/Cas system) to create a mutation via double stranded DNA break repaired by non-homologous end joining.

Finally, separate submission of a self-determination or request for EPA confirmation for purposes of the FFDCA exemption for a PIP proposed for use in food or feed is required only if it has not already been submitted under FIFRA. This is because the exemption eligibility determination process already requires the applicant to certify that the PIP meets the general qualifications for exemption, which includes exemption under the FFDCA for PIPs used in food or feed. We envision at least one scenario in which a developer may need to submit a self-determination or request for EPA confirmation for the purposes of FFDCA but not FIFRA. That scenario arises when residues of a PIP will be in or on food imported into the United States, but the PIP is not intended to be sold or distributed for pesticidal use (e.g., PIP containing seed or plant sold for planting) in the United States (and thus is not subject to FIFRA regulation).

2. Proposed process for a letter of self-determination for a PIP to qualify for exemption.

The Agency is proposing a new provision in Subpart E, 40 CFR 174.91, entitled "Submitting a letter of self-determination for exemption." The proposed provision describes the requirements and process of notifying EPA that the developer has determined (or "self-determined") that a PIP qualifies for exemption.

Self-determination letters may be submitted electronically (guidance for electronic submission can be found in Pesticide Registration Notice 2011-3 or any subsequent revision or replacement) or by paper submission. Proposed 40 CFR 174.91 includes information on how to format the letter and the required contents of the letter, including a statement certifying the developer's determination of exemption eligibility. If a developer does not have an EPA company number they will be required to obtain a company number prior to submission of a self-determination letter. EPA intends that self-determination letters will not be submitted under FIFRA section 33 (Pesticide Registration Improvement Extension Act of 2018 (PRIA)) and will

not be subject to application fees.

In addition, this provision explains that a developer must submit its letter of self-determination prior to engaging in activities subject to FIFRA for the proposed PIP (e.g., distribution and sale of the PIP at issue), and the exemption does not apply until EPA confirms receipt of the self-determination. EPA notes that the developer is responsible at all times for ensuring its self-determination is accurate and if at any time EPA determines that a self-determination was wrongly made, or is no longer accurate due to the availability of new information that was not available at the time the self-determination was made, EPA and the FDA can take action to protect public health or the environment. This includes the possibility of enforcement under FIFRA or FFDCA. For electronically submitted letters, this receipt confirmation occurs automatically upon submission and is considered equivalent to written confirmation of receipt. EPA will provide written confirmation of receipt within 30 days of receiving a self-determination letter via mail. EPA will notify FDA when it receives a letter of self-determination.

3. Proposed EPA confirmation submission process for a PIP to qualify for exemption.

The Agency is proposing a new provision in Subpart E, 40 CFR 174.93, entitled "Obtaining EPA confirmation of eligibility for the exemption." This provision describes the process through which a developer may seek confirmation from EPA whether a PIP meets the criteria for exemption codified in 40 CFR 174.21. A developer must submit information as outlined in 40 CFR 174.91 along with specific supporting documentation. For example, the information required to support the request for a PIP based on a sexually compatible plant created through biotechnology is described in proposed 40 CFR 174.95 and discussed in Unit VI.C.3. The provision also specifies that any claims of confidentiality for information submitted

in the request for EPA confirmation must be made in accordance with the procedures outlined in 40 CFR 174.9.

In addition, the provision at 40 CFR 174.93 explains that upon receipt of the request, EPA will review the submission and determine whether the PIP meets all necessary criteria to be exempt under 40 CFR 174.21. The Agency proposes to notify the submitter in writing of its determination. The exemption goes into effect only once the developer receives EPA's confirmation in writing, unless a self-determination letter was previously submitted. Once a decision has been made that a PIP meets the criteria for exemption, this decision applies to all requirements under FIFRA, except for the adverse effects reporting under 40 CFR 174.71. As described in Unit VI.C.1., exempt PIPs are still subject to 40 CFR 174.71 and EPA reserves the right to reassess whether a PIP meets the criteria for exemption should the Agency learn of relevant information subsequent to confirming its eligibility to be exempt under 40 CFR 174.21.

EPA intends for requests for EPA confirmation to be submitted using the current submission category (M009) and associated fee structure for a Non-FIFRA Regulated Determination under FIFRA section 33 (PRIA). Currently, under the Non-FIFRA Regulated Determination category, the statutory time for EPA to review and make a determination is 120 days. The logistics of the submission for a request and EPA review times may change in the future if PRIA changes or a different structure for submissions is adopted.

4. Proposed documentation for an exemption for PIPs based on sexually compatible plants created through biotechnology.

The Agency is proposing a new provision in Subpart E, 40 CFR 174.95, entitled "Documentation for an exemption for a plant-incorporated protectant based on a sexually compatible plant created through biotechnology." This proposed provision describes the specific

information that must be documented for any PIPs based on sexually compatible plants created through biotechnology for which a developer is claiming an exemption. This provision serves two purposes. First, the provision describes the information that must be submitted to EPA, pursuant to 40 CFR 174.93, for confirmation that a PIP meets the exemption criteria. Second, the provision describes the information that any developer must maintain for 5 years pursuant to the recordkeeping requirements set forth in 40 CFR 174.73.

For PIPs based on sexually compatible plants created through biotechnology, the Agency is proposing that the information documented for recordkeeping and submitted during a request for EPA confirmation contain three main information elements: (1) information on the biology of the plant; (2) a description of the pesticidal trait and how it was engineered; and (3) information on the molecular characterization of the PIP. The proposed information elements are necessary to ensure that the PIP based on a sexually compatible plant created through biotechnology meets the FIFRA and FFDCA proposed exemption criteria. Specifically, information that EPA proposes will be needed for each element is as follows.

The first proposed element, information on the biology of the plant, will include: the identity of the recipient plant, including genus and species; and if the PIP was derived from another plant species, the identity of the source plant, including genus and species, and information to demonstrate the recipient plant and the source plant are sexually compatible. EPA anticipates that information fulfilling the first element will typically be a narrative description to show that the PIP is found in plants that are sexually compatible with the recipient plant.

The proposed second element, description of the pesticidal trait and how it was engineered into the plant, will include a narrative description of the intended pesticidal function resulting from the modification of the plant and the technique used to make the modification

(e.g., was the Cas enzyme stably integrated during development and if so was it segregated out of the final product). This information ensures that no unapproved ingredients remain in the final product. In products where the recipient plant is a food plant in which the levels of the pesticidal substance are commonly screened for in conventional breeding to ensure safe levels, the second element requires that the developer describe how conventional breeding practices have been and will be performed on the product proposed for exemption. This criterion can be fulfilled with a confirmation that the developer has screened its product for acceptable levels of the pesticidal substance (e.g., generally accepted safe content for solanine is 20-25 mg/100g of fresh potato weight). This criterion ensures that levels of the pesticidal substance are not present in the recipient food plant, as the plant is grown and harvested under normal conditions of use, at levels that are injurious or deleterious to human health as stated in the FFDCA proposed exemption criteria.

The proposed third element, molecular characterization of the PIP, includes two components. First, EPA is proposing to require the nucleotide sequence and the amino acid sequence of the PIP in the recipient plant, including a sequence comparison between the recipient plant and the relevant comparator (i.e., the source plant if a source plant was used or the unmodified plant if no source plant was used). For a plant-incorporated protectant where the regulatory region has not been modified, the sequence information will confirm that this is true. For PIPs where the regulatory region of an existing or inserted native gene has been modified, the second component is EPA's proposal to require confirmation that the expression profile (i.e., tissues, developmental stages, and levels of expression) of the PIP is not outside that observed in plants that are sexually compatible with the recipient plant. In this circumstance, the developer must show that the highest level of expression of the PIP obtained under normal environmental

conditions across the lifespan of the plant does not exceed the upper limit observed in a plant that is sexually compatible with the recipient plant. EPA envisions that a developer can meet this requirement through either rationale or data confirmation: a developer can document a rationale regarding the expected phenotype given the type of modification made (e.g., is the modification meant to optimize an allele and therefore may result in a slight increase in expression but no change in expression pattern or has something more significant been done that could lead to altered expression patterns), or the developer can provide expression data examining the tissue/life stage in which expression is expected to be highest to corroborate its expectation. The extent of expression data required is expected to be directly correlated to the likelihood that the modification could lead to a novel expression profile. Information described under elements one through three will inform whether the PIP meets criteria (a) and (b) of proposed FIFRA exemption and criteria (a) and (b) of proposed exemption from the requirement of a tolerance.

D. What Are the Proposed Recordkeeping Requirements?

EPA proposes to add a new provision in Subpart D, 40 CFR 174.73, entitled "General recordkeeping requirements for exemptions." This section describes the documentation and recordkeeping that must be done for exempted PIPs listed under 40 CFR 174.21(d). Specifically, in order for a PIP listed under 40 CFR 174.21(d) to be eligible for exemption, a developer must submit to EPA either a self-determination letter or a request for EPA confirmation that the PIP is eligible for exemption prior to engaging in FIFRA regulated activities. Accordingly, proposed 40 CFR 174.73 mandates that the developer maintain documentation of such a submission along with supporting information. Supporting information would include the information listed in the exemption specific section of subpart E. This documentation would need to be maintained for five years starting from the effective date of the exemption. Finally, proposed 40 CFR 174.73

states that this information must be made available to EPA upon request. This request may occur as part of routine enforcement activities (e.g., auditing, inspections) conducted by EPA to ensure compliance with EPA regulations or subsequent to EPA receiving an adverse effects report.

E. What is the Proposed Clarification to General Qualifications for Exemptions?

In 2001, EPA developed "General Qualifications for Exemptions" at 40 CFR 174.21, which describes criteria that are required for any PIP to be exempt from the requirements of FIFRA, with the exception of the adverse effects reporting requirement at 40 CFR 174.71. These criteria were developed at the same time as the FIFRA and FFDCA exemptions for PIPs derived through conventional breeding and thus were drafted with reference to those specific sections. The Agency is proposing edits to 40 CFR 174.21 to clarify the applicability of this framework to other PIP exemptions, including the language in the proposal.

For paragraph (a), this revision simply clarifies that this paragraph is specific to the pesticidal substance of the PIP. This update is necessary to avoid confusion over the current dual use of the word "plant-incorporated protectant" in 40 CFR 174.21 to refer to both the pesticidal substance and the PIP as a whole, per the definition in 40 CFR 174.3. For paragraph (b), the current reference to sections 40 CFR 174.507 through 174.508 only allows for a PIP to be exempt if the residues of the PIP are nucleic acids or come from a sexually compatible plant. This restriction was established when the only exempt PIPs were from sexually compatible plants. EPA is proposing to revise paragraph (b) to refer to subpart W, rather than the specific sections. For paragraph (c), the current reference to 40 CFR 174.705 only allows for a PIP to be exempt if the inert ingredients are from sexually compatible plants. Again, this restriction was established when the only exempt PIPs were from sexually compatible plants. Although EPA is not proposing an inert ingredient exemption specific to this proposal, EPA believes it is

important to add flexibility to the regulatory text to allow PIPs to be exempt based on other inert ingredient exemptions that EPA may establish in subpart X in the future. Thus, EPA is proposing to revise paragraph (c) to refer to subpart X, rather than the specific section of 40 CFR 174.705. Finally, EPA proposes to add a new paragraph (d) to section 40 CFR 174.21 to account for the proposed exemption eligibility determination process (Unit VI.C.) and proposed recordkeeping requirements (Unit VI.D.). This paragraph specifies that for PIPs listed in the subsequent subparagraph (i.e., subparagraph (d)(i)), compliance with recordkeeping and providing an exemption eligibility determination to EPA is a requirement of the exemption. The addition of paragraph (d) does not impact the current exemption under section 40 CFR 174.25 for PIPs from sexually compatible plants, because PIPs from sexually compatible plants (or the proposed amended title, PIPs from sexually compatible plants through conventional breeding) are not identified in paragraph (d).

F. What is the Clarification of Exemptions for Sexually Compatible PIPs?

In 2001, EPA exempted one category of PIPs from all FIFRA requirements, with the exception of the adverse effects reporting requirement at 40 CFR 174.71. PIPs derived through conventional breeding from plants sexually compatible with the recipient plant were exempted from FIFRA, and a companion FFDCA exemption from the section 408 requirement of a tolerance for residues of this category of PIPs was also issued. Conventional breeding is defined at 40 CFR 174.3 as "the creation of progeny through either: the union of gametes, i.e., syngamy, brought together through processes such as pollination, including bridging crosses between plants and wide crosses, or vegetative reproduction. It does not include use of any of the following technologies: Recombinant DNA; other techniques wherein the genetic material is extracted from an organism and introduced into the genome of the recipient plant through, for

example, micro-injection, macro-injection, micro-encapsulation; or cell fusion."

The Agency is proposing to clarify the relationship between the proposal on PIPs based on sexually compatible plants created through biotechnology and the exemptions currently at 40 CFR 174.25, "Plant-incorporated protectant from sexually compatible plant," and 40 CFR 174.508 "Pesticidal substance from sexually compatible plant; exemption from the requirement of a tolerance." To this end, EPA would insert "created through conventional breeding" immediately after the subject of the exemption (e.g., "pesticidal substance") in each section title, and insert an additional criterion into 40 CFR 174.25 and 174.508 as follows:

"(c) The genetic material is transferred from the source plant to the recipient plant only through conventional breeding."

This clarification would explicitly state in the title and criteria at 40 CFR 174.25 and 174.508 the condition underlying the rationale for exemption offered in the preamble of the July 19, 2001 *Federal Register* notice implementing these paragraphs (66 FR 37772; July 19, 2001). Although 40 CFR 174.25 has always meant "only through conventional breeding," this is a necessary clarification now given that the proposed amended definition for "sexually compatible" states that "a viable zygote can be formed through the union of two gametes through conventional breeding," which would modify the existing definition that states that "a viable progeny is formed only through the union of two gametes through conventional breeding." The clarification would also explicitly indicate how proposed sections 40 CFR 174.26 and 174.541 on PIPs based on sexually compatible plants created through biotechnology relate to the existing exemptions for PIPs created through conventional breeding from sexually compatible plants at 40 CFR 174.25 and 174.508. The Agency is not proposing similar modifications at 40 CFR 174.705, and instead proposes to expand the scope of that exemption to include both

conventional breeding and biotechnology, as described in Unit VI.G.

G. What is the Proposed expansion of the inert ingredient exemption at 40 CFR 174.705 to include intermediary substances initiated through biotechnology?

1. *Description of the expansion*. EPA is proposing to expand the scope of the existing inert ingredient exemption at 40 CFR 174.705 to include inert ingredients that are intermediary substances initiated through biotechnology so long as they still meet the existing criteria. In the 2001 preamble promulgating 40 CFR 174, EPA stated "with regard to the enzymes, precursors, or intermediates in biosynthetic pathways necessary for anabolizing the pesticidal substance, EPA at this time considers them to be part of the plant-incorporated protectant because the substance is intended to "ensure the presence of the active ingredient"—i.e., it is an inert ingredient." Although the biochemical pathway may be initiated by a modification created through biotechnology, EPA believes the plant-produced intermediaries leading to the ultimate production of the pesticidal substance meet the scientific rationale of the existing inert ingredient exemption at 40 CFR 174.705. This is because EPA's proposed exemption at 40 CFR 174.26 provides developer flexibility by allowing changes to the nucleic acid sequence of the PIP as long as those modifications still result in the same pesticidal substances exempt under 40 CFR 174.25, thereby maintaining the integrity of such biochemical pathways described in the 2001 preamble. Therefore, although the technique used to initiate such a biochemical pathway may be different, the intermediary substances themselves remain the same.

2. *Risk analysis*. EPA believes the risk analysis at Unit VI.A.3. supporting the proposal for exemption from FIFRA requirements and the risk analysis at Unit VI.B. supporting the FFDCA section 408 proposal for exemption from the requirement of a tolerance also supports the exemption from FIFRA and the FFDCA for inerts that meet the criteria under the proposed

expansion of 40 CFR 174.705, because these substances would be endogenous to plants in sexually compatible populations and thus would not present novel exposures should inert ingredient intermediaries be initiated through a modification using biotechnology.

VII. Request for Comment

EPA is seeking public comment on all aspects of this proposed rule, including comments on the specific points discussed in this unit and the specific points raised in Units V. and VI. of this proposal.

A. What inert ingredients could be present in PIPs based on sexually compatible plants created through biotechnology?

An "inert ingredient" is defined in 40 CFR 174.3 to mean "any substance, such as a selectable marker, other than the active ingredient, where the substance is used to confirm or ensure the presence of the active ingredient, and includes the genetic material necessary for the production of the substance, provided that genetic material is intentionally introduced into a living plant in addition to the active ingredient." Additionally, in 2001 EPA stated that "with regard to the enzymes, precursors, or intermediates in biosynthetic pathways necessary for anabolizing the pesticidal substance, EPA at this time considers them to be part of the plant-incorporated protectant because the substance is intended to "ensure the presence of the active ingredient"—i.e., it is an inert ingredient." As stated in Unit VI.G., the Agency is expanding the current inert ingredient exemption at 40 CFR 174.705 to be inclusive of both conventional breeding and biotechnology in order to account for potential intermediary substances as described in the 2001 quote that would ultimately lead to the production of the pesticidal substance.

However, outside of these intermediary substances, the Agency does not anticipate other

types of inert ingredients (e.g., herbicide tolerance) in PIPs based on sexually compatible plants created through biotechnology. Previous biotechnology approaches that relied on DNA constructs were constructed with the genetic material encoding for both the active and the inert ingredient. These DNA constructs ensured that the inert ingredient could be used to confirm the plants or cells that successfully integrated the genetic material encoding for the active ingredient. However, to create PIPs based on sexually compatible plants created through biotechnology, modifications coding for non-pesticidal traits in transgenic PIPs (e.g., herbicide resistance) would instead be incorporated into the recipient plant genome independent of the active ingredient. Because these events occur independently the modification cannot confirm or ensure the presence of the active ingredient. The modification therefore would not meet the definition of an inert ingredient under 40 CFR 174.3 because it is an independent, non-pesticidal trait not regulated under FIFRA. EPA expects that any ingredients intentionally added during the development of PIPs based on sexually compatible plants created through biotechnology that are specific to the production of the active ingredient (e.g., guide RNA, DNA nuclease) and that could function as an inert ingredient would either be transiently transformed or would be removed (e.g., through segregation of the trait) during the breeding process and that if these ingredients have not been removed from the final product the product would not meet the criteria at proposed under the new 40 CFR 174.26 and would not qualify for the new exemptions.

The Agency therefore requests comment on whether there are any inert ingredients other than the intermediary substances described in the 2001 quote that will remain in the final plant products containing PIPs based on sexually compatible plants created through biotechnology. If inert ingredients other than the intermediary substances described in the 2001 quote are identified in the responses to the previous request, the Agency also requests comment as to

whether the inert ingredients in PIPs based on sexually compatible plants created through biotechnology require the proposal of an exemption that would be specific to those created through biotechnology and would allow developer flexibility in the nucleic acid sequence. If the Agency receives comments that indicate inert ingredients other than the intermediary substances described in the 2001 quote may be present in the final plant product and/or that developer flexibility in the nucleic acid sequence of inert ingredients would be beneficial, the Agency will consider finalizing the proposed rule with exemptions under FIFRA and FFDCA for inert ingredients derived through biotechnology from sexually compatible plants. These exemptions would be based on the proposed exemptions 40 CFR 174.26 and 174.541 in that the use of biotechnology is permitted and only inert ingredients composed of genetic material that is derived from sexually compatible plants would be exempt. The Agency is not currently considering an exemption for potential inert ingredients that are derived from sources that are not sexually compatible with the recipient plant (e.g., Cas proteins).

B. What process should EPA use to provide notice that a PIP no longer meets the criteria for exemption if new information is provided?

EPA is proposing to exempt PIPs based on sexually compatible plants created through biotechnology from regulation under FIFRA, except for the adverse reporting effects at 40 CFR 174.71. In the event EPA learns of information that affects a previous determination that a PIP based on a sexually compatible plant created through biotechnology meets the criteria, EPA will reconsider the new information and provide a new determination in writing whether the PIP continues to meet the criteria for exemption. EPA requests comment on whether the process outlined is detailed enough.

C. Should EPA consider other approaches for its confirmation process?

EPA is proposing that the exemption of PIPs based on sexually compatible plants created through biotechnology include a process through which developers of PIPs based on sexually compatible plants created through biotechnology submit either a self-determination letter or request confirmation that their PIP meets the criteria for exemption. EPA seeks comment on whether the Agency should consider different approaches for its proposed exemption eligibility determination process. For example, one alternative process could be to require mandatory EPA confirmation so that all developers must submit information to EPA for EPA confirmation that their PIP meets the exemption criteria prior to engaging in activities subject to FIFRA. EPA requests comment on whether or how such a mandatory approach could be workably implemented, and whether such an approach would be useful or justified.

This alternative process would follow the same submission procedures that are outlined in proposed 40 CFR 174.93, and the information required to determine the eligibility of exemption would remain the same as outlined in proposed 40 CFR 174.95. Another alternative could be a voluntary confirmation process for all PIP products exempted under the proposed rule similar to that in USDA's final rule titled "Movement of Certain Genetically Engineered Organisms." (85 FR 29790; May 18, 2020). Only those developers who seek EPA's confirmation would be required to submit to the Agency information and data sufficient to establish that their PIPs are eligible under the proposed exemptions. Developers who do not seek EPA confirmation would not be required to submit any documentation to EPA (and thus this alternative would be different from EPA's proposed process through which developers submit either a self-determination letter or request confirmation that their PIP meets the criteria for exemption). EPA requests comment on whether or how such a voluntary approach could be workably implemented (e.g., should the recordkeeping requirements at proposed 40 CFR 174.73 be required for

developers who do not submit for EPA confirmation) and whether such an approach would be useful or justified?

D. Is EPA's intent behind the use of the terms "native" and "never derived" clear?

The Agency is proposing to define "native gene" to mean "a gene that is identified in the recipient plant or plants that are sexually compatible with the recipient plant; and has never been derived from a source that is not sexually compatible with the source plant." The phrase "has never been derived from a source that is not sexually compatible with the source plant" is meant to clarify that a PIP would not qualify for the proposed exemption if the gene was introduced into the genome of the source plant through transgenic technology, as those genes may not be representative of the shared genetic information between sexually compatible plants. For example, bacterial endotoxin genes (e.g., from the source *Bacillus thuringiensis*) are a commonly engineered pesticidal trait, but EPA does not intend for these genes to be considered part of the sexually compatible gene pool nor does EPA intend for these genes to qualify for the proposed exemption. However, EPA is also aware that horizontal gene transfer from *Agrobacterium* to plants can occur and that in some cases, like the domesticated sweet potato, it may result in a variant so commonly found that it could be considered part of the gene pool. It is the Agency's intent to exclude substances that plant breeders do not have experience with (e.g., a bacterial endotoxin not found in a food plant) from the proposed exemption. Given the explanation of the intent behind the terms "native" and "never derived," EPA seeks comment on whether the intent behind the use of the terms is clear. The Agency also seeks comment on whether alternative phrasing rather than "native" would be more appropriate. Similarly, the Agency seeks comment on whether a definition for "native gene" or "native allele" is necessary, or if the criteria included in these definitions should instead be incorporated into the exemption text.

E. Should EPA issue a clarifying exemption for loss-of-function traits that result in pesticidal effects?

As described in Unit II.A., the Agency considers the modification of existing genes in a plant to elicit a loss-of-function trait in order to confer a pesticidal effect to be a pesticide. EPA recognizes that this scenario is different from transgenic PIPs that traditionally produce a pesticidal substance, e.g., PIPs that produce a protein or other substance that kill a pest. In many instances, for loss-of-function traits, the genetic material of the recipient plant has been altered to reduce the production of a substance that would otherwise facilitate the susceptibility of that plant to a pathogen; therefore, the reduction or elimination of that substance has a mitigating or pesticidal effect. For PIPs created through conventional breeding, EPA considers these loss-of-function traits to be included in the existing exemption at 40 CFR 174.25. It is also EPA's intention that loss-of-function traits created through biotechnology are included under the proposed exemption at 40 CFR 174.26 so long as the exemption criteria are met (e.g., only substances produced that are found in sexually compatible plants).

In situations where the existing plant genes are acting as the pesticidal substance, EPA recognizes that it can be confusing under the current regulatory definitions in 40 CFR 174.3 to interpret the pesticidal substance and the genetic material necessary for the production of the pesticidal substance as applying to the same thing. Given that it is potentially confusing to refer to both of these as a "pesticidal substance" interchangeably, EPA requests comment as to whether a clarifying exemption specific to "loss-of-function PIPs," where the genetic material is the pesticidal substance, would aid in reducing ambiguity over the use of the term "pesticidal substance" in the regulatory text. EPA proposes to accomplish this by separating exempt PIPs into two categories, those where the gene product is the pesticidal substance and those where the

genetic material itself is the pesticidal substance. Similar to the existing exemption at 40 CFR 174.25 and the proposed exemption at 40 CFR 174.26, the clarifying exemption specific to loss-of-function PIPs would be written to limit permissible modifications to those that do not result in the production of a modified substance. In other words, only the reduced expression of an unmodified protein or the elimination of the unmodified protein would be permissible. This is to ensure 1) limitation of substances to only those with which plant breeders have experience, 2) the applicability of EPA's risk assessment for the exemption at 40 CFR 174.25 and the risk assessment for the proposed exemption at 40 CFR 174.26 to the proposed "loss-of-function PIPs" exemption, and 3) that if the reduced substance is in fact a pesticidal substance (or its reduction leads to an increase of another substance that is pesticidal) it is covered by either the existing tolerance exemption at 40 CFR 174.508 or the proposed tolerance exemption at 40 CFR 174.541. It is also important to note that when the loss of function of a gene intentionally results in the increase in production of another gene which ultimately produces a pesticidal substance, this PIP would fall under either the existing exemption at 40 CFR 174.25 or the proposed exemption at 40 CFR 174.26. If EPA were to issue an exemption for loss-of-function PIPs, EPA would no longer include the category at proposed 40 CFR 174.26(a)(2)(iv). In addition, EPA also requests comment on how a separate exemption or exemptions (if any) specific to loss-of-function PIPs might be implemented. Should such a separate exemption(s) be technique-specific (e.g., should it be specific to loss-of-function PIPs created through conventional breeding?) or should there be one exemption that covers loss of function PIPs regardless of the technique used in their creation?

VIII. References

The following is a listing of the documents that are specifically referenced in this

document. The docket includes these documents and other information considered by EPA, including documents that are referenced within the documents that are included in the docket, even if the referenced document is not physically located in the docket. For assistance in locating these other documents, please consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

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IX. Statutory and Executive Order Reviews

Additional information about these statutes and Executive orders can be found at *https://www.epa.gov/laws-regulations/laws-and-executive-orders*.

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review

This action is a significant regulatory action that was submitted to the Office of Management and Budget (OMB) for review under Executive Orders 12866 (58 FR 51735, October 4, 1993) and 13563 (76 FR 3821, January 21, 2011). Any changes made in response to OMB recommendations have been documented in the docket for this action as required by section 6(a)(3)(E) of Executive Order 12866.

B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Costs

This action is expected to be an Executive Order 13771 deregulatory action. Details on the estimated cost savings of this proposed rule can be found in EPA's cost analysis (Ref. 2).

C. Paperwork Reduction Act (PRA)

The information collection activities in this proposed rule have been submitted for approval to OMB under the PRA, 44 U.S.C. 3501 *et seq*. The Information Collection Request (ICR) document that EPA prepared is assigned EPA ICR No. 2619.01. You can find a copy of the ICR in the docket for this rule, and it is briefly summarized here.

The information collection activities in this proposed rule are associated with the proposed exemption eligibility process (i.e., self-determination or request for EPA-confirmation, and associated recordkeeping) that would be made available as an alternative to the existing pesticide registration and tolerance activities that are already approved by OMB under OMB Control No. 2070-0060 (EPA ICR No. 0277). As such, the ICR accompanying this proposed rule

is intended to amend that existing ICR at the final rule stage, incorporating the information collection activities for the exemption and related estimated burden.

Respondents affected entities: See Unit I.A.

Respondent's obligation to respond: Mandatory to obtain the exemption (40 CFR part 174, as proposed)**.**

Estimated number of respondents: 1.

Frequency of response: Once.

Total estimated burden: 14 hours (per EPA determination). Burden is defined at 5 CFR 1320.3(b).

Total estimated cost: $1,487 (per EPA determination), includes $0 annualized capital or operation & maintenance costs.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control numbers for EPA's regulations in 40 CFR are listed in 40 CFR part 9.

Submit your comments on the Agency's need for this information, the accuracy of the provided burden estimates, and any suggested methods for minimizing respondent burden to EPA using the docket identified at the beginning of this rule. You may also send your ICR-related comments to OMB's Office of Information and Regulatory Affairs via email to *OIRA_submission@omb.eop.gov*, Attention: Desk Officer for the EPA. Since OMB is required to make a decision concerning the ICR between 30 and 60 days after receipt, OMB must receive comments no later than [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. EPA will respond to any ICR-related comments received on the proposed ICR amendment when issuing the final rule.

D. Regulatory Flexibility Act (RFA)

Pursuant to the RFA section 605(b), 5 U.S.C. 601 *et seq*., I hereby certify that this action will not have a significant economic impact on a substantial number of small entities. In making this determination, EPA believes that the impact of concern is any adverse economic impact, and that an agency may certify that a rule will not have a significant economic impact on a substantial number of small entities if the rule relieves regulatory burden, has no net burden, or otherwise has a positive economic effect on the small entities subject to the rule. The factual basis for this determination is presented in the small entity impact analysis prepared as part of the cost analysis for this proposed rule (Ref. 2), which is summarized in Units I.E. and VI.A.4., and a copy is available in the docket for this rulemaking. The following is a brief summary of the factual basis for this certification.

The effect of the rule is to reduce costs to developers of PIPs based on sexually compatible plant created through biotechnology, and the cost savings per product are approximately $444,000 – $459,000. The cost savings per product would be realized when a letter of self-determination is sent. The proposed exemption for PIPs based on sexually compatible plants created through biotechnology reduces the cost associated with meeting regulatory requirements and so removes a potential barrier to market entry for small entities. Of the entities likely to develop PIPs based on sexually compatible plants created through biotechnology, EPA currently estimates that approximately 80% are small entities. We have therefore concluded that this action will relieve regulatory burden for all directly regulated small entities.

Any comments regarding the potential impacts on small entities from this action should be submitted to the Agency in the manner specified under **ADDRESSES**.

E. Unfunded Mandates Reform Act (UMRA)

This action does not contain an unfunded mandate as described in UMRA, 2 U.S.C. 1531-1538, and does not significantly or uniquely affect small governments. The action is not expected to impose an enforceable duty on any state, local or tribal governments, and the requirements imposed on the private sector are not expected to result in annual expenditures of $100 million or more for the private sector. Accordingly, EPA has determined that the requirements of UMRA sections 202, 203, 204, or 205 do not apply to this action.

F. Executive Order 13132: Federalism

This action does not have federalism implications as specified in Executive Order 13132 (64 FR 43255, August 10, 1999). It will not have substantial direct effects on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Thus, Executive Order 13132 does not apply to this proposed rule.

G. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

This action does not have tribal implications as specified in Executive Order 13175 (65 FR 67249, November 9, 2000). It will not have substantial direct effects on tribal governments, on the relationship between the Federal government and the Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes. Thus, Executive Order 13175 does not apply to this proposed rule.

H. Executive Order 13045: Protection of Children from Environmental Health Risks and Safety Risks

EPA interprets Executive Order 13045 (62 FR 19885, April 23, 1997) as applying only to those regulatory actions that concern environmental health or safety risks that EPA has reason to

believe may disproportionately affect children, per the definition of "covered regulatory action" in section 2-202 of the Executive Order. This action is not subject to Executive Order 13045 because it does not establish an environmental standard intended to mitigate a health or safety risk.

I. Executive Order 13211: Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use

This action is not a "significant energy action" as defined in Executive Order 13211 (66 FR 28355, May 22, 2001) because it is not likely to have a significant adverse effect on the supply, distribution, or use of energy.

J. National Technology Transfer Advancement Act (NITAA)

NTTAA section 12(d), 15 U.S.C. 272 note, does not apply to this proposed action because it would not impose any technical standards requiring Agency consideration of voluntary consensus standards. This regulation proposes the types of information to be submitted in a self-determination letter or EPA confirmation request concerning the exemption of PIPs based on sexually compatible plants created through biotechnology, but does not propose to require specific methods or standards to generate that information.

K. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

EPA believes that this action is not subject to Executive Order 12898 (59 FR 7629, February 16, 1994) because it does not establish an environmental health or safety standard.

L. FIFRA Review Requirements

In accordance with FIFRA section 25(a), EPA submitted the draft proposed rule to the Secretary of the United States Department of Agriculture (USDA) and the FIFRA Scientific

Advisory Panel (SAP) for review. A draft of the proposed rule was also submitted to the appropriate Congressional Committees.

M. Executive Order 13874: Modernizing the Regulatory Framework for Agricultural Biotechnology Products

This action is intended to further implement section 4(b) of Executive Order 13874 (84 FR 27899, June 11, 2019). If this proposal is made final, the final rule may promote future innovation and competitiveness by efficiently exempting through regulation qualifying PIPs based on sexually compatible plants created through biotechnology that meet the FIFRA and FFDCA standards for exemption.

List of Subjects in 40 CFR Part 174

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Plant-incorporated protectants, Reporting and recordkeeping requirements.

_____

Andrew Wheeler,

Administrator.

Therefore, it is proposed that 40 CFR chapter I be amended as follows:

Part 174--[AMENDED]

1. The authority citation for part 174 continues to read as follows:

Authority: 7 U.S.C. 136–136y; 21 U.S.C. 321(q), 346a and 371.

2. Amend § 174.3 by adding in alphabetical order the following definitions to read as follows:

§ 174.3 Definitions

* * * * *

Gene, and other grammatical variants such as "genic," means a functional unit of heritable genetic material that is comprised of the genetic material necessary for the production of a substance.

* * * * *

Native allele means a variant of a native gene that is identified in the genetic diversity of plants sexually compatible with the recipient plant.

Native gene means a gene that is identified in the recipient plant or plants sexually compatible with the recipient plant; and has never been derived from a source that is not sexually compatible with the source plant.

* * * * *

Sexually compatible, when referring to plants, means a viable zygote can be formed through the union of two gametes through conventional breeding.

* * * * *

3. Revise § 174.21 to read as follows:

§ 174.21 General qualifications for exemptions.

A plant-incorporated protectant is exempt from the requirements of FIFRA, other than the requirements of § 174.71, if it meets the exemption criteria in paragraphs (a) through (d) of this section. Plant-incorporated protectants that are not exempt from the requirements of FIFRA under this subpart are subject to all the requirements of FIFRA.

(a) The pesticidal substance from the plant-incorporated protectant meets the exemption criteria listed in at least one of the sections in §§ 174.25 through 174.50.

(b) When the plant-incorporated protectant is intended to be produced and used in a crop used as food, the residues of the pesticidal substance of the plant-incorporated protectant are either exempted from the requirement of a tolerance under FFDCA (21 U.S.C. 321 *et seq*.) as listed in subpart W of this part, or no tolerance would otherwise be required.

(c) Any inert ingredient that is part of the plant-incorporated protectant is listed as an approved inert ingredient in subpart X of this part.

(d) For plant-incorporated protectants listed in the subparagraphs below, the exemption applies only if the developer is compliant with the general record keeping requirements specified in § 174.73 and only after compliance with the relevant eligibility determination procedures specified in § 174.90:

(1) Plant-incorporated protectant based on a sexually compatible plant created through biotechnology.

(2) [Reserved]

4. Amend § 174.25 by:

a. Revising the section heading;

b. Revising the introductory paragraph; and

c. Adding paragraph (c).

The revisions read as follows:

§ 174.25 Pesticidal substance from a plant-incorporated protectant from a sexually compatible plant created through conventional breeding.

The pesticidal substance from a plant-incorporated protectant from a sexually compatible plant created through conventional breeding is exempt if all of the following conditions are met:

* * * * *

(c) The genetic material is transferred from the source plant to the recipient plant only through conventional breeding.

5. Add § 174.26 to read as follows:

§ 174.26 Pesticidal substance from a plant-incorporated protectant based on a sexually compatible plant created through biotechnology.

The pesticidal substance from a plant-incorporated protectant based on a sexually compatible plant created through biotechnology is exempt if all of the following conditions are met:

(a) The pesticidal substance is created through biotechnology from either an insertion of new genetic material as discussed in paragraph (a)(1) of this section or a modification of existing genetic material as discussed in paragraph (a)(2) of this section.

(1) A native gene is engineered into a non-genic location of the recipient plant genome, resulting in a pesticidal substance identical to the pesticidal substance identified in the source plant.

(2)(i) The existing native gene in the recipient plant is modified to alter the

amount of pesticidal substance produced without altering the identity of the pesticidal substance produced; or

(ii) The genetic material that encodes the substance of the existing native gene is modified to result in a pesticidal substance that is identical to the pesticidal substance encoded by a native allele of that gene; or

(iii) The existing genetic material is modified pursuant to both (i) and (ii).

(iv) The existing native gene in the recipient plant is modified to lose function through the reduction or elimination of the substance encoded by that gene.

(b) The pesticidal substance is not expressed at higher levels, in different tissues, or at different developmental stages than identified in a plant that is sexually compatible with the recipient plant.

(c) This exemption does not apply until the requirements in subpart E of this part have been met.

6. Add § 174.73 to read as follows:

§ 174.73 General recordkeeping requirements for exemptions.

For 5 years, starting with the effective date of a plant-incorporated protectant exemption, any person who produces an exempt plant-incorporated protectant listed under § 174.21(d) must do both of the following:

(a) Maintain documentation of either the letter of self-determination or the request for EPA confirmation along with all supporting documentation for the specific exemption listed in subpart E.

(b) Make the documentation of exemption eligibility available to EPA upon request.

7. Amend subpart E to read as follows:

Subpart E – Exemption Eligibility Determination Process and Requirements

§ 174.90 Determining Eligibility for Exemption

(a) *Options for determining eligibility*. For a plant-incorporated protectant listed under § 174.21(d), the developer must do at least one of the following actions to be eligible for the exemption in § 174.21:

(1) *Self-determination*. A developer may submit a letter of self-determination in accordance with § 174.91.

(2) *Request for EPA confirmation of eligibility*. A developer may submit a request for EPA confirmation of eligibility in accordance with § 174.93.

(b) *Where to submit a letter of self-determination or request for EPA confirmation*. A letter of self-determination or a request for EPA confirmation of eligibility must be submitted to the Office of Pesticide Programs' Document Processing Desk at the appropriate address as set forth in § 150.17(a) or (b) of this chapter, with the relevant "Attention" line: "Attention: Plant-Incorporated Protectant Exemption Self-Determination" or "Attention: Plant-Incorporated Protectant Request for Confirmation of Exemption Eligibility." [placeholder for future instructions covering electronic submissions].

(c) *Overlapping determinations of eligibility*. A developer may elect to submit a letter of self-determination as well as a request for EPA confirmation of eligibility concurrently or at a later time. If the developer so elects, the letter of self-determination will remain in effect while EPA evaluates the request for confirmation of eligibility.

(d) *Revisiting eligibility determination*. If, at any time after the letter of self-

determination is submitted or EPA issues a confirmation of eligibility, EPA becomes aware of information indicating that the exempt plant-incorporated protectant no longer meets the criteria for exemption (e.g., adverse effects reports submitted under § 174.71) or that the self-determination was incorrect, EPA will notify the original submitter in writing of EPA's intention to initiate a review of eligibility for exemption and may request additional information from the developer in order to evaluate that eligibility for exemption. Upon conclusion of its review, EPA will notify the developer in writing of its determination whether the plant-incorporated protectant meets the exemption criteria and any actions that will be required should the plant-incorporated protectant be found to not meet the exemption criteria. Under those circumstances, the plant-incorporated protectant may be considered to be noncompliant with FIFRA and subject to possible enforcement by EPA.

(e) *Extension of exemption to subsequent variations of the plant-incorporated protectant*.

(1) *Plant-incorporated protectant based on a sexually compatible plant created through biotechnology*. A letter of self-determination or EPA's confirmation that the plant-incorporated protectant based on a sexually compatible plant created through biotechnology meets the criteria for exemption applies to subsequent engineering of that plant-incorporated protectant by the submitter into other varieties of that same plant species as long as the submitter is doing one of the following:

(i) Producing the identical substance as in the exempt plant-incorporated protectant, so long as no modifications were made to the regulatory regions.

(ii) Creating the same phenotype as in the exempt plant-incorporated protectant

by targeting the same nucleic acid sequence in the regulatory region to result in a mutation via double-strand DNA break repaired by non-homologous end joining.

(iii) For subsequent engineering events that do not meet either criterion (e)(1)(i) or (1)(ii), a letter of self-determination or request for EPA determination must be submitted.

(2) [Reserved]

§ 174.91 Submitting a letter of self-determination for exemption.

A developer who elects to self-determine eligibility for the exemption of a plant-incorporated protectant listed under § 174.21(d) must comply with all of the following requirements.

(a) *When to submit a letter of self-determination*. A letter of self-determination for an exemption must be submitted to EPA prior to engaging in activities subject to FIFRA.

(b) *Contents of a letter of self-determination*. The letter of self-determination must:

(1) Provide the name and contact information for the submitter (including phone and email address), company name, or other affiliation.

(2) Identify the plant-incorporated protectant and the following exemption-specific information for the exemption for which eligibility is self-determined:

(i) *Plant-incorporated protectant based on a sexually compatible plant created through biotechnology*. Cite the paragraph under §§ 174.26 or 174.541 that is applicable to the PIP (i.e., (a)(1), (a)(2)(i), (a)(2)(ii), (a)(2)(iii), or (a)(2)(iv)).

(ii) [Reserved]

(3) Include the following statement of certification, filling in the information

described in italics:

> "I, [*name of submitter*], on behalf of [*name of company*] am submitting this Plant-Incorporated Protectant Exemption Self-Determination consistent with the provisions of 40 CFR part 174. I hereby confirm that the plant-incorporated protectant known as [*name of the plant-incorporated protectant*] is eligible under 40 CFR 174.21 to be exempt from the requirements of FIFRA, other than the requirements of 40 CFR 174.71 and 174.73. I understand that it is a violation of 18 U.S.C. 1001 to willfully make any false statement to EPA. I further understand that if this self-determination is not consistent with the provisions of 40 CFR part 174, this plant-incorporated protectant product may not be exempt from the requirements of FIFRA, and [*name of company*] may be subject to enforcement actions and penalties under FIFRA sections 12, 13, and 14, 7 U.S.C. 136j, 136k, and 136l. Moreover, I also understand that if this self-determination is not consistent with 40 CFR part 174, the residues of this plant-incorporated protectant may not be exempt from the requirement of a tolerance under the FFDCA, and [*name of company*], as well as foods containing such residues, may be subject to enforcement actions and penalties under Chapter III of the FFDCA, 21 U.S.C. 331 *et seq*."

(4) The statement must be dated and signed by an authorized representative of the developer of the plant-incorporated protectant.

(c) *EPA response*. For electronic submissions, EPA will provide electronic confirmation of receipt immediately. Electronic confirmation shall be equivalent to written confirmation. For submissions by mail, written confirmation of receipt within 30 business days of receipt of a letter of self-determination.

(d) *Effective date of exemption*. The exemption does not apply until EPA confirms receipt of the letter of self-determination.

§ 174.93 Obtaining EPA confirmation of eligibility for the exemption.

A developer who elects to request EPA confirmation of eligibility for exemption of a plant-incorporated protectant listed under § 174.21(d) must comply with all of the following requirements.

(a) *When to submit a request for EPA confirmation*. Unless the developer has received confirmation of receipt of a letter of self-determination, the request for EPA

confirmation must be submitted prior to engaging in activities subject to FIFRA.

(b) *Contents of a request for EPA confirmation of exemption eligibility*. The request must contain information as specified in § 174.91(b) and supporting documentation demonstrating that the plant-incorporated protectant meets the criteria for the exemption, as specified in exemption-specific sections of this subpart. Any claims of confidentiality for information submitted in the request for EPA confirmation must be made in accordance with the procedures outlined in § 174.9 of subpart A.

(c) *EPA review and response*. Upon receipt of a request, EPA will review and evaluate the information provided to determine whether the plant-incorporated protectant meets the exemption criteria in § 174.21. EPA may require additional information to assess whether a plant-incorporated protectant meets the criteria for exemption. EPA will notify the submitter in writing of its determination. If EPA determines that the plant-incorporated protectant does not meet the criteria for exemption, EPA will notify the submitter in writing of any actions that will be required.

(d) *Effective date for the EPA confirmed exemption*. If the plant-incorporated protectant is not already exempt pursuant to the self-determination process under § 174.91, this exemption **applies** once EPA notifies the submitter in writing, confirming that the plant-incorporated protectant meets the criteria for exemption.

§ 174.95 Documentation for an exemption for a plant-incorporated protectant based on a sexually compatible plant created through biotechnology.

A developer requesting EPA confirmation of exemption eligibility for a plant-incorporated protectant from a sexually compatible plant created through biotechnology pursuant to § 174.93 must submit the information in the following paragraphs to EPA

along with its request for exemption confirmation. Any developer required to maintain records under § 174.73 must maintain the following documentation.

(a) Biology of the plant.

(1) The identity of the recipient plant, including genus and species.

(2) If the plant-incorporated protectant was derived from another plant species, provide the identity of the source plant including genus and species and information to demonstrate the recipient plant and the source plant are sexually compatible.

(b) Description of the pesticidal trait and how the trait was engineered into the plant. If the pesticidal substance is a known mammalian toxin or toxicant (e.g., solanine) describe how conventional breeding practices are being used to ensure it does not exceed safe levels in the recipient food plant.

(c) Molecular characterization of the plant-incorporated protectant.

(1) The nucleotide sequence and the amino acid sequence of the plant-incorporated protectant in the recipient plant, including a sequence comparison between the recipient plant and the relevant comparator (i.e., the source plant if a source plant was used or the unmodified plant if no source plant was used).

(2) For a plant-incorporated protectant where the regulatory region of an existing or inserted native gene has been modified, confirmation that the expression level does not exceed that found in a sexually compatible plant and the plant-incorporated protectant is not expressed in tissues or developmental stages outside of that observed in a plant that is sexually compatible with the recipient plant.

8. Amend § 174.508 by:

a. Revising the section heading,

b. Revising the introductory paragraph,

c. Designating paragraph (c) as paragraph (d), and

d. Adding a new paragraph (c).

These revisions read as follows:

§ 174.508 Pesticidal substance from a plant-incorporated protectant from a sexually compatible plant created through conventional breeding; exemption from the requirement of a tolerance.

Residues of a pesticidal substance from a plant-incorporated protectant from a sexually compatible plant created through conventional breeding are exempt from the requirement of a tolerance if all the following conditions are met:

* * * * *

(c) The genetic material is transferred from the source plant to the recipient plant only through conventional breeding.

(d) The residues of the pesticidal substance are not present in food from the plant at levels that are injurious or deleterious to human health.

9. Add § 174.541 to read as follows:

§ 174.541 Pesticidal substance from a plant–incorporated protectant based on a sexually compatible plant created through biotechnology; exemption from the requirement of a tolerance.

Residues of a pesticidal substance from a plant-incorporated protectant based on a sexually compatible plant created through biotechnology are exempt if all of the following conditions are met:

(a) The pesticidal substance is created through biotechnology from either an

insertion of new genetic material as discussed in paragraph (1) or a modification of existing genetic material as discussed in paragraph (2).

(1) A native gene is engineered into a non-genic location of the recipient plant genome, resulting in a pesticidal substance identical to the pesticidal substance identified in the source plant.

(2)(i) The existing native gene in the recipient food plant is modified to alter the amount of pesticidal substance produced without altering the identity of the pesticidal substance produced; or

(ii) The genetic material that encodes the substance of the existing native gene is modified to result in a pesticidal substance that is identical to the pesticidal substance encoded by a native allele of that gene; or

(iii) The existing genetic material is modified pursuant to both (i) and (ii).

(iv) The existing native gene in the recipient plant is modified to lose function through the reduction or elimination of the substance encoded by that gene.

(b) The residues of the pesticidal substance are present only in tissues and developmental stages identified in a plant that is sexually compatible with the recipient food plant, and do not exceed levels found within that plant, as long as those levels are not injurious or deleterious to human health.

(c) This exemption does not apply until the requirements in subpart E of this part have been met.

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